Evaluation of the usefulness of C-reactive protein as a marker of urinary tract infection, and its response to treatment in persons with spinal cord injury

Dissertation submitted to

The Tamil Nadu Dr. M.G.R. Medical University

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CERTIFICATE

This is to certify that the dissertation titled “Evaluation of the usefulness of C-reactive protein as a marker of urinary tract infection and, its response to treatment in persons with spinal cord injury” is the bona fide work of Dr. Ranjan S S, candidate number **201529052** towards the MD Physical Medicine and Rehabilitation Degree Examination of the Tamil Nadu Dr. M.G.R Medical University to be conducted in May 2018. This work has not been submitted to any university in part or full.

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DECLARATION

I hereby declare that this dissertation titled “Evaluation of the usefulness of C-reactive protein as a marker of urinary tract infection and, its response to treatment in persons with spinal cord injury” is a bona fide work done by me under the guidance of Dr. Henry Prakash M, Professor, Department of Physical Medicine and Rehabilitation, Christian Medical College, Vellore. This work has not been submitted to any university in part or full.

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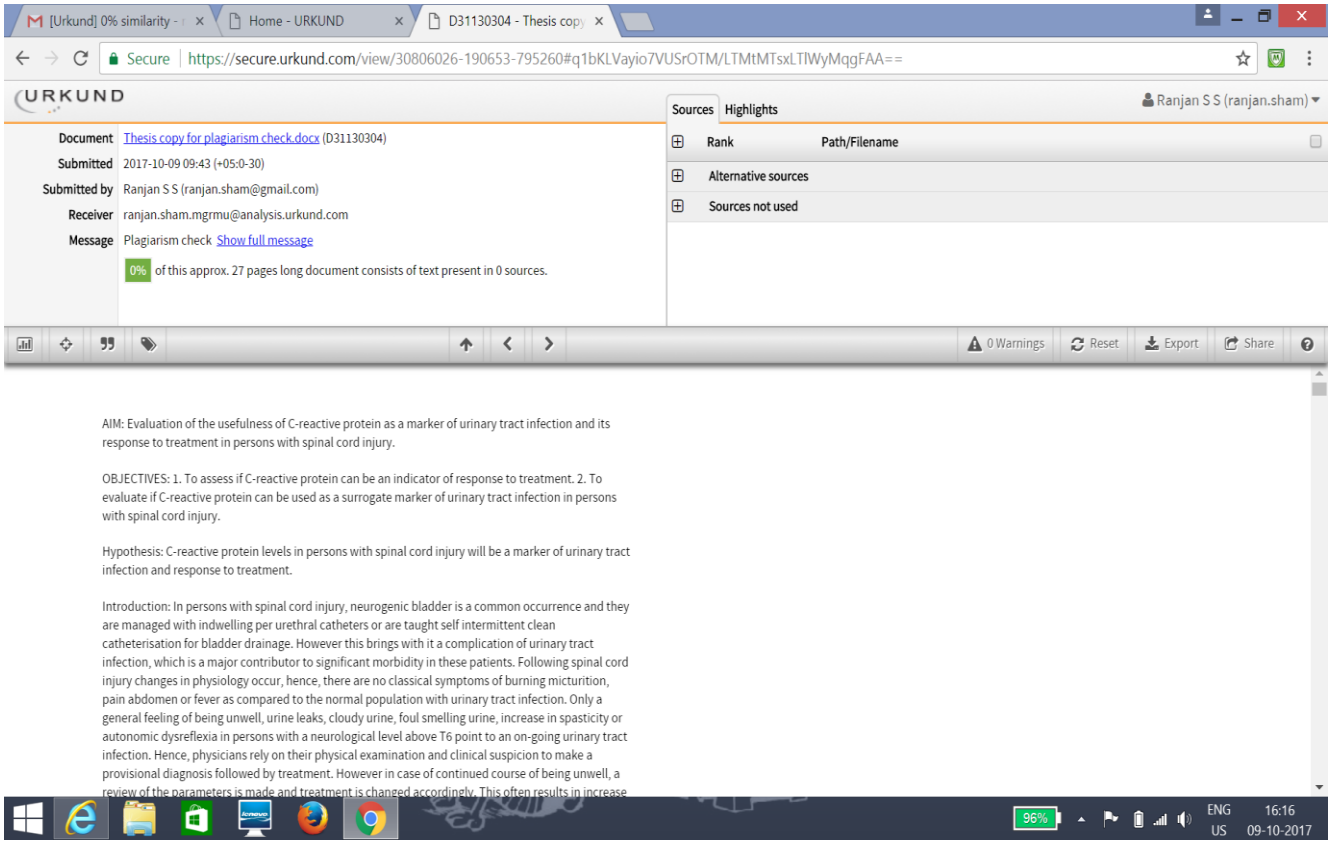
PLAGIARISM CHECK CERTIFICATE:



CERTIFICATE – II

This is to certify that this dissertation work titled "Evaluation of the usefulness of C-reactive protein as a marker of urinary tract infection and, its response to treatment in persons with spinal cord injury" of the candidate Dr. Ranjan S S with registration Number **201529052** for the award of MD in the branch of Physical Medicine and rehabilitation. I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows zero (0%) percentage of plagiarism in the dissertation.

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Abbreviations:

SCI – Spinal cord injury

UTI – Urinary tract infection

CIC – Clean intermittent catheterisation

CRP – C-reactive protein

TWBC/TC – Total white blood cell

AIM: Evaluation of the usefulness of C-reactive protein as a marker of urinary tract infection and its response to treatment in persons with spinal cord injury.

OBJECTIVES:

1. To assess if C-reactive protein can be an indicator of response to treatment.
2. To evaluate if C-reactive protein can be used as a surrogate marker of urinary tract infection in persons with spinal cord injury.

Hypothesis: C-reactive protein levels in persons with spinal cord injury will be a marker of urinary tract infection and response to treatment.

Introduction:

In persons with spinal cord injury, neurogenic bladder is a common occurrence and they are managed with indwelling per urethral catheters or are taught self intermittent clean catheterisation for bladder drainage. However this brings with it a complication of urinary tract infection, which is a major contributor to significant morbidity in these patients.

Following spinal cord injury changes in physiology occur, hence, there are no classical symptoms of burning micturition, pain abdomen or fever as compared to the normal population with urinary tract infection. Only a general feeling of being unwell, urine leaks, cloudy urine, foul smelling urine, increase in spasticity or autonomic dysreflexia in persons with a neurological level above T6 point to an on-going urinary tract infection. Hence, physicians rely on their physical examination and clinical suspicion to make a provisional diagnosis followed by treatment.

However in case of continued course of being unwell, a review of the parameters is made and treatment is changed accordingly. This often results in increase in the length of stay in the hospital, treatment cost and significant emotional trauma to the patient. This study aims to see if C-reactive protein can be a surrogate marker of UTI and if it is a marker for response to treatment.

Review of literature:

Spinal cord injury (SCI) is the damage to spinal cord that causes changes in its function, either temporary or permanent. These changes translate into loss of muscle function, sensation, or autonomic function. Depending on the location and severity of damage along the spinal cord, the symptoms can vary widely, from pain or numbness to paralysis to incontinence of the bladder and bowel. Complications that can occur in the short and long term after injury include muscle atrophy, pressure sores, urinary tract infections, and respiratory problems.

The earliest recorded spinal cord injuries and its complications was found in "Edwin Smith Papyrus" written in 17th century BC which described spinal cord injury as an injury that cannot be healed.(1)

Worldwide, the incidence (number of new cases) of SCI ranges from 10.4 to 59 people per million per year.(2) The estimated prevalence (number of people living with SCI) ranges from 236 per million in India to 1800 per million in the US.(3)
Males account for the majority of traumatic spinal cord injuries. Most of these injuries occur in men under 30 years of age.(4) The high numbers of injuries are attributable in a large part to road traffic accidents and sports injuries.(5) Traumatic SCI, mostly affects cervical vertebrae approximately 50% followed by thoracic and then lumbosacral vertebrae. C5 segment is the most common lesion level followed y C4, C6, T2, C7 and L1. (6)

Non traumatic causes of spinal cord injury are as shown in the table below(7) :

Table no. 1: Non-traumatic causes of spinal cord injury

Neoplasm	Primary and metastatic tumours
Infections	TB spine, HIV myelopathy, Osteomyelitis of the spine
Inflammatory	Transverse myelitis
Vascular	AV malformation, spinal cord hypoperfusion, embolization, thrombus
Degenerative	Spondylosis
Collagen vascular diseases	Systemic lupus erythematosus, Sjogren syndrome
Others: Toxic-metabolic disorders Radiation Multiple sclerosis Neurosarcoidosis	Nutritional disorders Decompression sickness Neuromyelitis optica Para neoplastic syndromes

Complications of spinal cord injury;

Complications are abundant in patients after spinal cord injury. Respiratory system complications are the leading cause of death in the first year following injury. They account for 37% of deaths and 21% of deaths after the first year in a large cohort taken in Model SCI care Systems and Shriner's Hospitals.(8) Cardiac complications and septicaemia usually caused by urinary tract infections, infected pressure ulcers and respiratory tract infections are second and third respectively. (9)

Genito-urinary complications after SCI are common and was the leading cause of death three decades ago, which has considerably decreased probably due to the scientific advances in management of the urological symptoms. The urologic complications seen after spinal cord injury are secondary to neurogenic bladder which include urinary tract infections, prostatitis, hydronephrosis, epididymoorchitis, urethral erosions and strictures, renal and bladder calculi, penoscrotal fistulas, bladder carcinoma and renal failure.(9) In the Model Spinal Cord Injury Systems Database, USA, rehospitalisation occurred in 55% of patients in the first year after SCI.(10) Genitourinary and respiratory complications and pressure ulcers were the most common reasons for hospitalization. Advanced patient age along with spinal cord injury also added on the risk of complications requiring hospitalization.

Complications of spinal cord injury are given in the table below:

Table no. 2: Complications of SCI

System involved	Complications
Pulmonary	Pneumonia, atelectasis, respiratory failure, pleural complications, Deep vein thrombosis, pulmonary embolism
CNS	Nerve entrapment syndromes, post-traumatic syringomyelia or cystic myelopathy, tethering of cord, late compression of cord, neuropathic joints
Gastrointestinal	Adynamic ileus, impaired evacuation of bowel, higher incidence of plaques, gingivitis, gastric erosions, gastric and duodenal ulcers, gall stones, pancreatitis
Endocrine	Low testosterone in males, increased risk of Diabetes mellitus type II, nocturnal enuresis due to altered diurnal rhythm of ADH secretion
Others	Autonomic dysreflexia Pressure ulcers Disorder of sexuality and fertility Anemia Psychiatric complications

The urinary system – Anatomy and physiology:

The urinary system is divided into upper and lower urinary tract. Upper urinary tract consists of the kidneys and the ureters and the lower urinary tract consists of the bladder, internal and the external urethral sphincter and the urethra.

The upper urinary tract filters the end products of metabolism and excess fluid and excretes it in the form of urine into the lower urinary tract through the ureters, mainly into the bladder. The kidneys consist of millions of nephrons which along with the collecting tubules form the structural unit of the kidney. Each nephron is further made of a renal corpuscle which filters the plasma, a renal tubule which selectively absorbs water from the filtrate to form urine. The collecting ducts collect the urine from the renal tubules and open into a terminal papillary duct which empties into a minor calyx at the apex of the renal papilla. The urine from the renal papillae flow out into the urinary bladder through the ureters. (11)

The urinary bladder is a muscular structure that acts as reservoir for the urine excreted through the kidneys. It is lies in the lesser pelvis and distends as urine collects and expands antero-superiorly. It has a fundus, base, neck, apex, one superior and two infero-lateral surfaces.(11)

The bladder has four layers: serous, muscular, sub-mucous and mucous coats. The serous layer originates from the peritoneum. The muscular layer consists of three smooth muscular fibres: external longitudinal fibres, middle circular fibres and an internal layer of longitudinal fibres. The external layer consists of Detrusor muscle. The fibres of the middle circular layer form the internal urethral sphincter. The two

bands of oblique fibres which originate behind the orifices of the ureters maintain the obliquity of the ureters during bladder contraction and prevent urine reflux into the bladder. The sub-mucous layer connects the muscular and mucosal layer. Transitional epithelium covers the mucosal layer.(12)

The Urethra is a tubular structure that extends from the internal urethral orifice in the bladder to the external urethral orifice. In males it measures about 18-20cm and 4cm in females. In males it is further divided into proximal bulbar urethra surrounded by the bulbo-spongiosus muscle and distal penile component, the prostatic urethra which is surrounded by the prostate and the membranous urethra which is the shortest portion and, with the exception of the external urethral orifice is the narrowest part of the canal. It measures about 2cm and pierces the urogenital diaphragm. It is surrounded by the fibres of the external urethral sphincter. The urethra is lined by mucous membrane which is supported by a sub-mucous tissue. The mucous membrane is in continuity with that of the bladder, ureters and kidneys.(12)

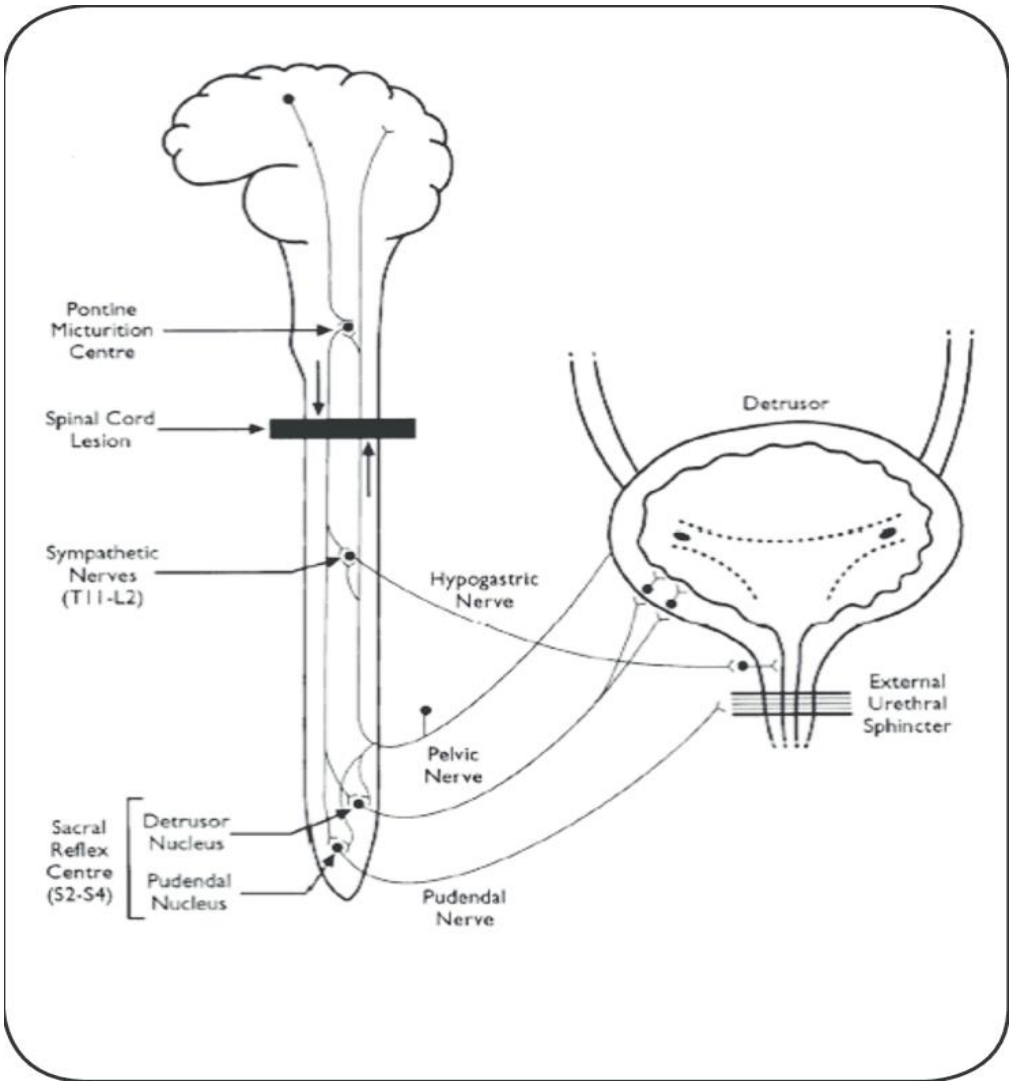
Mechanism and control of micturition:

The lower urinary tract is innervated by sympathetic, parasympathetic and somatic nerves through hypogastric, pelvic nerves and the pudendal nerves respectively, as illustrated in figure no.1.

The sympathetics arise from the thoraco-lumbar outflow and supply through the hypogastric and pelvic nerves. The parasympathetic neurons arise from the sacral centres and their axons in the pelvic nerves synapse with postganglionic fibres in the intramural vesical ganglia. Somatic motor centre is situated in the Onuf's nucleus in

the ventral horn of the sacral spinal cord and supply the external sphincter through the pudendal nerve.

Figure 1: Anatomy of micturition



Axons of small myelinated A-delta fibres or unmyelinated C fibres carry the sensory afferents which pass through the pelvic nerves whose cell bodies are situated in the sacral root ganglia. Pontine micturition co-ordinates the synergistic detrusor-external urethral sphincter function.(13)

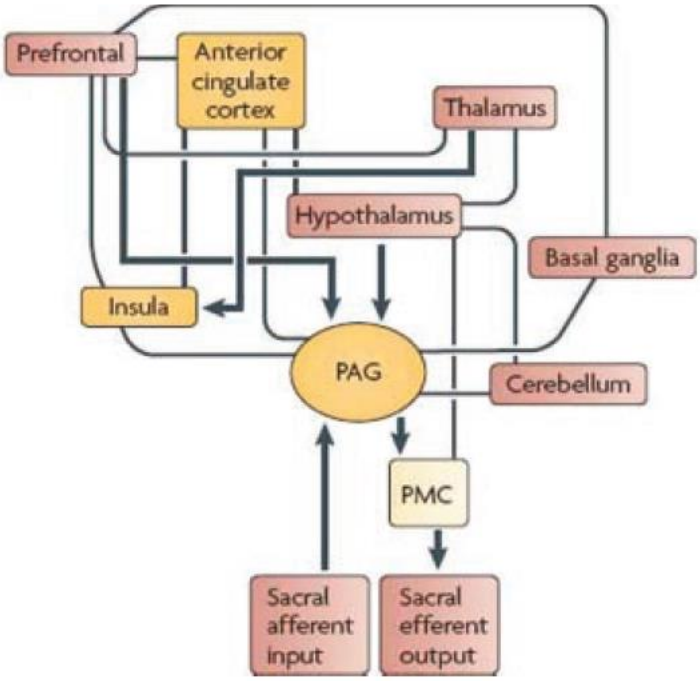
Spinal neurons which control the lower urinary tract function are situated in the dorsal commissure, superficial dorsal horn and parasympathetic nucleus.

The excitatory transmitter is Glutamate and inhibitory neurotransmitters are Gamma amino butyric acid and Glycine. (14)

Supraspinal structure involved in the control of micturition are medullary dorsomedial pontine tegmentum, also called as pontine micturition center or the Barrington nucleus, the Raphe nucleus, Locus ceruleus, periaqueductal gray (PAG) matter, hypothalamus and the medial frontal cortex.

The data obtained from Positron Emission Tomography (PET) and function magnetic Resonance Imaging (fMRI), brain regions that are activated during lower urinary tract function have been mapped and the "Bladder control matrix" described as in figure 2. (14)

Figure 2: Control of micturition



In the storage phase of micturition, afferent signals are sent to the periaqueductal gray (PAG) area and are relayed through the hypothalamus to the anterior cingulate cortex, the insula and the prefrontal cortex. The prefrontal cortex, hypothalamus, insula and anterior cingulate cortex inhibit the PAG and thereby inhibiting the pontine micturition centre. The PAG inhibition by the prefrontal cortex is interrupted when a decision to void is made and the hypothalamus stimulates the PAG and the pontine micturition centre which send excitatory signals to the sacral spinal cord leading to the contraction of the detrusor and relaxation of the urethra.(14)

Receptors and neurotransmitters that line the bladder wall are muscarinic, nicotinic, alpha and beta adrenergic receptors. The cholinergic muscarinic M2 and M3 receptors are widely distributed in the body of the bladder, the trigone, bladder neck and the urethra. M2 receptors are more in number but M3 receptors are more important

functionally. Cholinergic nicotinic receptors are mainly located in the striated sphincter.(13)

Alpha-1 adrenergic receptors are located primarily in the trigone, bladder neck and the urethra. Subgroups of Alpha 1 receptors have been identified, which may assist in increased specificity with regard to therapeutic agents. Nor-epinephrine secreting nerve cells are found in the paravesical and intramural ganglia. These cells have an excitatory effect and maintain continence by contraction of the bladder neck and urethral smooth muscle. Beta 2 and 3 adrenergic receptors found in the body and neck of the bladder are inhibitory and produce relaxation bladder neck on initiation of voiding and relax the bladder to store urine during the filling phase.(13)

Nor-epinephrine is the main effector transmitter for urethral contraction via Alpha 1 receptors and urethral smooth muscle relaxation is achieved by the action of acetylcholine in the pelvic ganglia. This releases nitric oxide which leads to the relaxation of the muscle. Prostaglandins also have a relaxation effect on the urethral smooth muscle. Serotonin causes urethral muscle contraction which might be important in treating open bladder neck or lax external urethral sphincter.(13)

In the brainstem and spinal cord, neurotransmitters have inhibitory or excitatory effects based on their site of action. Serotonin may have inhibitory detrusor effect in the midbrain, which is suggested by how serotonin blockers like tricyclics which are used to treat nocturnal enuresis. Opiate receptor activation in the brainstem and spinal cord inhibits voiding. Serotonin and nor-epinephrine re-uptake inhibitors prolong their effect in the Onuf's nucleus leading to increased activity of the external urethral sphincter.

Neurogenic bladder after SCI:

Neurogenic bladder is a term applied to a malfunctioning urinary bladder due to neurologic dysfunction or insult emanating from internal or external trauma, disease, or injury. Most commonly seen following spinal cord injury, either due to trauma or non-traumatic causes.

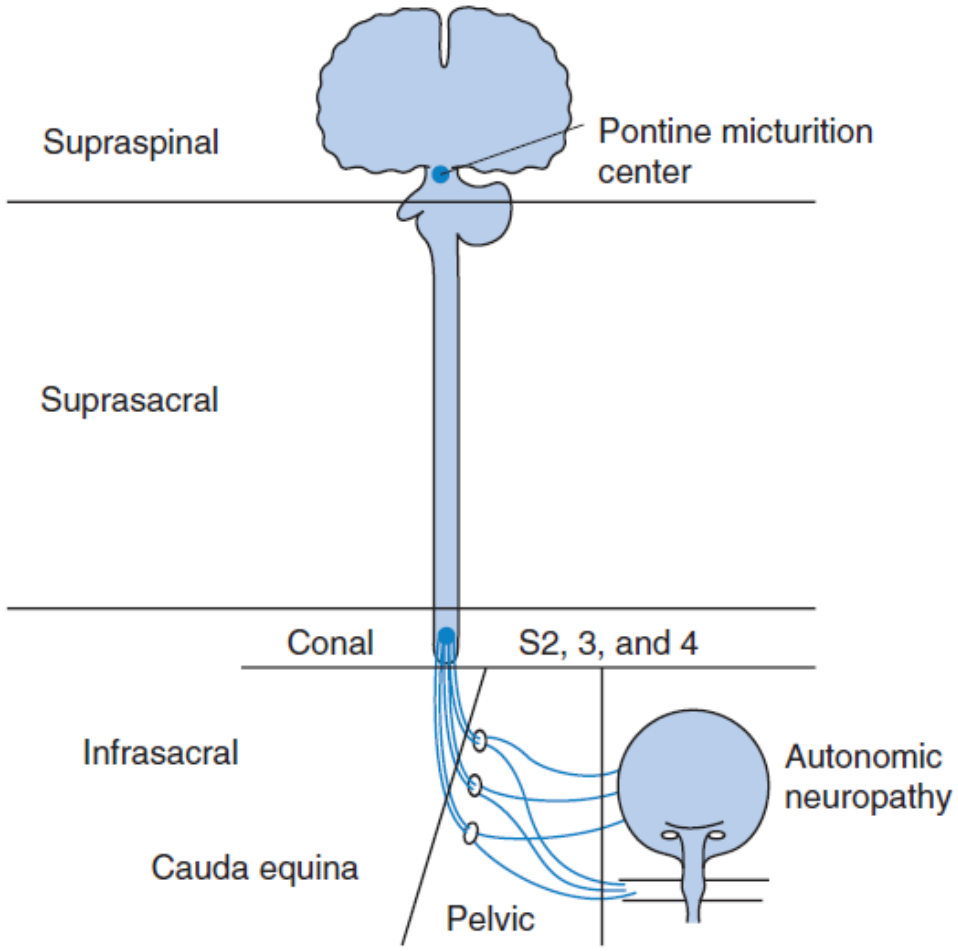
Wallerian degeneration is seen in the injured nerve endings in the spinal cord, where the glial cells produce a scar which prevents the growth of the neuron.(15)

The outcome of the injury on the lower urinary tract depends on the etiology, level of injury, duration and severity of the injury. Following spinal cord injury there is a period of bladder areflexia leading to urinary retention, the duration of which depends on the time period of the spinal shock phase which can vary from few hours to few weeks.(16) Initiation of micturition reflex is by activation of low threshold A–delta fibres normally, but after SCI, micturition reflex depends on Capsaicin sensitive C-fibres, which has been demonstrated by intrathecal Capsaicin which reduced the bladder overactivity.(17) The altered physiology of the lower urinary tract and the micturition reflex leads to frequent urinary tract infection and other related complications.

Classification of neurogenic bladder is done in various ways. They are:

1. Anatomic classification of Bors and Comarr. It is done on the basis of the anatomic level of injury, as shown in the figure below.

Figure 3: Anatomic classification



2. Functional classification is based on cystometric findings, and has five basic groups as described: (1) reflex, (2) uninhibited, (3) autonomous, (4) motor paralytic and (5) sensory neurogenic bladders. It is based on the conventional urodynamic study findings according to the passive storage ability of the bladder and activity and co-ordination of the detrusor and sphincter.

Functional classification is mentioned in the table below:

Table no.3: Functional classification

Type of failure	**Bladder factors**	**Outlet factors**
Failure to store	Detrusor overactivity	Denervated pelvic floor
	Decreased compliance	Bladder neck descent
		Intrinsic bladder neck sphincter failure
Failure to empty	Acontractile detrusor	Detrusor-sphincter dyssynergia
	Hypocontractility	Non relaxing voluntary sphinchter Mechanical obstruction (Benign prostatic hypertrophy or stricture)

In practice, it is common to use a combination of both anatomic and functional classifications. Clinical management is based on functional changes demonstrated by urodynamic testing. (13)

Management of Neurogenic bladder:

Careful history and a meticulous examination herald the management of neurogenic bladder.

Lower urinary tract symptom classification:

According to the International Continence Society – Fact sheet, 2015 the lower urinary tract symptoms are classified in terms of bladder storage problems, voiding symptoms and post micturition symptoms.(18)

Storage symptoms:

They include daytime frequency and nocturia which are experienced during the storage phase.

Increased day time frequency is when a patient complains that he/she considers that they void too often by day.

Nocturia is when a person has to wake up once or more than once to void at night.

Urgency is when is there is a sudden compelling desire to pass urine which is difficult to postpone.

Urinary incontinence is the involuntary leakage of urine.

Stress urinary incontinence is involuntary leakage of urine on exertion like coughing, sneezing or lifting weight.

Urge incontinence is when there is involuntary urine leakage that accompanies or precedes urgency.

Mixed urinary incontinence is when involuntary urine leakage is associated with urgency and exertion.

Nocturnal enuresis is loss of urine during sleep.

Continuous urinary incontinence is continuous leakage of urine.

Bladder sensation is defined by:

Normal is when the person is aware of bladder filling and increasing sensation up to a strong desire to void.

Increased is when the person has an early and persistent desire to void.

Reduced is when the person is aware of bladder filling but does not feel a desire to void.

Absent is when the person has no sensation of bladder filling or desire to void.

Non-specific is when the person has no specific bladder sensation but perceive bladder fullness as abdominal fullness, or spasticity.

Voiding symptoms:

They are experienced during the voiding phase.

Slow stream is when the person feels that his or her perception of reduced urine flow on voiding, when compared to previous performance or to others.

Splitting or spraying of the urine stream.

Intermittent stream is when the urine flow stops and starts, on one or more occasions, during micturition.

Hesitancy is when there is difficulty in initiating micturition causing delay in the onset of voiding after the person is ready to pass urine.

Straining is when muscular effort is required to initiate, maintain or improve the urinary stream.

Terminal dribble is when at the final part of micturition the flow has slowed to a trickle/dribble.

Post micturition symptoms

Symptoms which are experienced immediately after micturition are called post micturition symptoms.

Feeling of incomplete emptying is a term which is self-explanatory for a feeling experienced by a person after voiding.

Post micturition dribble is there is involuntary loss of urine immediately after voiding, for example like after leaving the toilet in men and immediately after rising from the toilet seat, for women.

Lower urinary tract pain symptoms:

Abnormal sensations felt by the patient include pain, pressure and discomfort. Pain can be felt during various phases of the bladder cycle. It should be characterised type, frequency, duration, precipitating and relieving factors and also by location.

Bladder pain is pain felt suprapubically or retropubically, and increases with bladder filling and may persist with voiding.

Urethral pain is pain felt in the urethra.

Vulval pain is felt in and around the external genitalia.

Vaginal pain is felt internally, above the introitus.

Scrotal pain can be localised to the testis or epididymis, cord structures or scrotal skin.

Perineal pain is felt between the posterior fourchette and the anus in females and between the scrotum and anus in males.

Pelvic pain is less well defined and is less clearly related to micturition cycle or bowel function and is not localised to any organ.(18)

Presenting symptoms:

The presenting symptoms of neurogenic bladder depend on the etiology of the injury, site, duration and extent of the injury, and neurologic recovery after the initial trauma. After the spinal shock phase, in an upper motor neuron type of bladder, symptoms would be varying degrees of impaired bladder sensation and

ability to void, intermittent non-stress urinary incontinence, hesitancy, straining, urgency, diminished or interrupted stream, sensation of incomplete voiding. In lower motor neuron type of bladder, the symptoms would be that of bladder sensation, inability to void normally, stress urinary incontinence and necessity to apply abdominal pressure to empty the bladder. There may also be history of pressure ulcers related to inadequate perineal hygiene and/or recurrent urinary tract infection. The history should include the following(19) :

1. Premorbid voiding pattern
2. Lower urinary tract symptoms
3. Bladder sensation
4. Type of voiding – mode, frequency, difficulties
5. Incontinence
6. Relevant review of systems

Physical examination:

A meticulous and detailed neurological examination including deep tendon reflexes, clonus and plantar responses in lower limbs and sensory examination including sacral dermatomes which include perianal sensation, deep anal pressure, voluntary anal contraction and bulbo-cavernous reflex in males and clitoro-cavernous reflex in females, must be done. (13)

Bladder diary:

A regular bladder diary should be maintained. Micturition time chart which records the time of each micturition timing, a frequency volume chart which

records the voided volumes should be maintained. Further relevant symptoms like urgency, pain, incontinence episodes and pad usage is added in the diary. Average voided volume, voiding frequency, day/night urine production and nocturia can be recorded from the bladder diary. This information helps in obtaining an objective verification of symptoms, and provides control values for subsequent urodynamic studies to prevent over filling of the bladder.(13)

Diagnostic tests:

Urologic testing is individualised to each patient depending on their symptoms and neurologic condition. Lower urinary tract evaluation can range from urinalysis to urine culture to measurement of post-void residual volume. If there is incomplete voiding, recurrent urinary tract infection or upper tract changes are present then a full urodynamic evaluation maybe required.

The urodynamic results are not condition specific and cannot be used to determine the level of neurologic lesion. For instance, a suprasacral neurogenic bladder in a complete spinal cord injury can be areflexic and a Cauda-equina bladder may exhibit high pressures and low compliance. Urodynamic study should be used to confirm the type of bladder that is determined by clinical examination.(16)

Upper tract tests:

Ultrasonography (US)

Ultrasonography is a low cost and low risk test or evaluation of upper tract but it is not sensitive to evaluate acute ureteral obstruction, for which other investigations maybe required. US is adequate for imaging chronic obstruction, dilation, scarring, renal

mass (both cystic and solid), and renal calculi. A filled bladder can be visualised and can be evaluated for wall thickness, irregularity, and presence of bladder calculi.

Plain radiography of the kidneys, ureter and bladder

Kidneys, ureters and bladder (KUB) X-ray combined with US can aid in identifying calculi that are not visualised in the US alone.

Computed tomography

CT scan without contrast agent of the KUB is useful in evaluation of the upper tracts when there is acute obstruction of the ureters due to calculi. It is the most sensitive investigation to detect small bladder, ureteral and renal calculi.

Excretory urography / Computed tomography / Intravenous pyelogram

A CT scan without and then with intravenous contrast and with a delayed plain KUB X ray has replaced excretory urogram. It is contraindicated in patients whose serum creatinine is more than 1.5mg/dL, or if the patient has insulin dependent diabetes mellitus, as the contrast can increase the risk in contrast induced nephropathy. Alternative studies like US, radioisotope renography, and cystoscopy with retrograde pyelography is indicated in such patients.(13)

Creatinine clearance time

It is a gold standard test for assessing renal function and is said to approximate the glomerular filtration rate(13). Its accuracy depends on meticulous urine collection. It can be inaccurate in spinal cord injury patients with reduced muscle mass.

Isotope studies

The Technetium-99m dimercaptosuccinic acid (DMSA) scan is used for differential function and evaluation of the functioning area of the renal cortex.(20)

Technetium-99m mertiatide (MAG-3) renogram gives information about urinary tract drainage and a good assessment of differential function. In patients with suspected ureteral reflex, these tests must be done after the bladder has been drained with an indwelling catheter. Iothalamate can also be used in excretory urography.(21)

Lower urinary tract tests:

Urinalysis, culture and sensitivity testing

These tests are done for patients with neurogenic bladder and should be repeated as necessary. These are recommended before any invasive procedures and in cases of symptomatic urinary tract infection or appearance of any new symptoms like increased leaks, frequency, etc. Bacteruria should be treated before any invasive urologic procedure.(13)

Postvoid residual urine (PVR)

Volume of urine remaining in the bladder after voiding is an indicator of the quality of voiding, and is a simple tool to assess lower urinary tract symptoms.(22)

Low PVR of less than 20% of bladder capacity by itself is not an indicator of balanced bladder as high intravesical pressure can be present despite low PVR. PVR is simple to determine and clinically useful when compared with previous recordings and in conjunction with bladder pressure, clinical symptoms and appearance of the bladder wall. PVR s can vary throughout the day. PVR can be obtained by inserting a catheter or by ultrasonography.(13)

Cystography

It is the test conducted to know the presence of vesicoureteric reflux. Cystography can be conducted by retrograde cystography, voiding cystourethrography, radionuclide cystography.(23) It also shows the bladder outline and shape. Video-urodynamic study, including fluoroscopy of the bladder and intravesical pressure, is more useful in some cases.

Cystometrography (CMG)

Cystometrography is a bladder filling study, but only very little information is obtained about the voiding phase of bladder function. Carbon dioxide (CO2) can be used as the filling agent in the commercial available appliance, but this method of

testing has shown considerable variation, poor reproducibility and presence of artifacts.(24) Two channel catheters are used to obtain water CMGs, one for filling the bladder and the other for pressure recording. A rectal pressure trace helps in distinguishing intravesical pressure variations resulting from intra-abdominal transmission from detrusor contractions. Filling rates vary from 20ml to 100ml per minute. International continence society recommends the use of the terms 'Physiological' and 'Non-physiological' rates of filling. Physiological filling rate is the filling rate less than the predicted maximum filling rate (predicted maximum body weight in Kg divided by 4, expressed as ml/min). Non-physiological filling rate is filling rate more than the predicted maximum filling rate.(18) Patients are asked to suppress voiding during filling. Normal bladder capacity values range from 300-600ml. Initial sensation of filling occurs approximately at 50% of the bladder capacity. The sensation of normal fullness is perceived in the lower abdomen and as sense of urgency in the perineum. The bladder's compliance is derived by the change in volume divided by the increase in baseline pressure during filling in the absence of a detrusor contraction. It is should be greater than 10mL/cm H20 and 10-20 Ml/cm H20 is considered as borderline if the bladder capacity is reduced. Any involuntary detrusor contraction during the test, is identified as any appreciable phasic pressure change, is considered abnormal. These contractions are referred as detrusor overactivity if the patient is neurologically intact. These contractions are called as neurogenic detrusor overactivity if the patient has a suprasacral or supraspinal lesion.

Patients with neurogenic bladder can be instructed to void at capacity but many are unable to generate a detrusor contraction. The presence of involuntary detrusor

contraction confirms the presence of detrusor hyperactivity in a patient with suprasacral or supraspinal lesion, but the absence of the same is not necessarily an indication of bladder areflexia in a patient with infrasacral lesion. CMG is a useful test to confirm the return of detrusor reflex in spinal shock phase and presence of detrusor hyperactivity in patients with supraspinal or suprasacral lesion before pharmacotherapy is started.(13)

Urethral pressure profiles

They are measured by withdrawing a measuring device, which is a micro tip transducer or perfused side-hole catheter, gradually down the urethra and measuring the centrally acting forces. It has very limited role, except in determining whether a sphincter-active area is still present after sphincterotomy.

Sphincter electromyography

Sphincter electromyography (EMG) is combined with CMG or video-urodynamic study. Needle and surface electrodes placed over the levator muscle, perianal or periurethral muscles, have been used to record EMG.(25) The integrated EMG recordings are displayed along with the bladder pressure. EMG activity increases gradually as the bladder capacity is reached during filling and then becomes silent just before voiding. In complete spinal cord injury, low levels of EMG activity with no recruitment during the filling phase are commonly seen. When there is a reflex detrusor contraction in these patients, the EMG activity in the sphincter might increase than decrease. In detrusor-sphincter dyssynergia, voiding occurs at the end of detrusor

contraction as the striated sphincter relaxes more quickly than the smooth muscle of the bladder. Denervation is diagnosed with a standard needle EMG.

Videourodynamics

Videourodynamics gives maximum information about the filling and voiding phases of lower urinary tract. It is indicated in patients with incontinence, those who can void voluntarily but have sensation of incomplete voiding, patients with mechanical obstruction and neuropathy, and prior to sphincterotomy. In addition to detecting detrusor sphincter dyssynergia, it is useful to assess detrusor contraction and the presence or absence of bladder neck obstruction. A two channel catheter is placed in the bladder and a balloon catheter is placed in the rectum for the study. Sphincter EMG can be recorded along with bladder, detrusor (bladder minus rectal) and rectal pressures. A contrast solution is delivered at 50mL/min is used to fill the bladder, with the patient sitting or lying. Fluoroscopy is used to monitor the bladder image intermittently and the radiographic and urodynamic image is mixed on the same screen and can be recorded on videotape. The flow rate can be recorded if the patient can sit and void during the study.(13)

Cystoscopy

Long term indwelling urethral or suprapubic catheterisation increases the risk for changes in the bladder mucosa and rarely tumour development, which is about 0.39% in persons with SCI.(26) Cystoscopy is recommended after 5 years in high risk

patients, such as smokers, or after 10 years if there are no risk factors. Repeated lower urinary tract infections are an indication for cystoscopy to rule out bladder calculi and presence of foreign bodies like hairs, which are introduced by catheterisation.(13)

Uroflometry

It measures the flow rate of the external urinary stream in volume per unit time in millilitres per second (ml/s). It is a relatively inexpensive and non-invasive procedure. It is a first line screening test for patients with lower urinary tract symptoms who can void.(27)

Urodynamic measurement provides an objective and qualitative information about the storage and voiding symptoms of the patient. Patient should be provided adequate privacy and should be asked to void when they feel a ‘‘normal’’ desire to void. Patients should be asked if their voiding was representative of their usual voiding pattern. Automated data analysis must be verified and artifacts removed and mentioned. Uroflometry results should be compared with the data in the bladder diary of the patient. Estimation of post void residual volume completes the non-invasive assessment of voiding function.(28)

COMPLICATIONS OF NEUROGENIC BLADDER

Till the mid-20th century, neurogenic bladder related complications were the leading cause of morbidity and mortality in spinal cord injury patients.

Better management techniques have resulted in decreased mortality in patients with neurogenic bladder, though significant complications are still attached to neurogenic bladder.(29)

Urinary tract infection

Urinary tract infection is seen in majority of the patients with neurogenic bladder. Risk factors being poor bladder emptying and post void residual volume. Epididymo-orchitis, seminal vesiculitis, prostatitis, epididymitis, and orchitis are seen in patients on long term catheterisation due to blockage of the ejaculatory and prostatic ducts. Symptomatic UTI is less common than asymptomatic catheter associated bacteruria.

There is no strong evidence that states that among patients using intermittent catheterisation, incidence of UTI is affected by use if sterile or clean technique, single or multiple use catheters, coated or uncoated catheters or any other strategy.(30) Urethral strictures and false passages become increasingly common with long term use of intermittent catheterisation. Good patient education and good compliance by the patient in the use of proper material and technique, plays an important role in reducing the complications.(31)

Vesicoureteric reflux

It is a condition in which there is reflux of urine from the bladder into the ureters. Cystogram and videourodynamic study is used to diagnose vesicoureteric reflux. In patients with neurogenic bladder, it is an indicator of failure to maintain optimal bladder pressure – volume profile. In 17-15% of suprasacral SCI patients reflux is seen. It can occur in any form of bladder management. Persistent reflux can cause repeated UTIs and may predispose to formation of bladder calculi and lead to renal deterioration and also death subsequently due to severe renal compromise in SCI patients.(32)

Hydronephrosis

Increased pressure in a poorly compliant bladder can cause dilatation of the upper tract with or without vesicoureteric reflux and can lead to significant morbidity and mortality. In neurogenic bladder, reflux further contributes to hydronephrosis. Detrusor sphincter dyssynergia, bladder calculi and any other obstruction to the ureters may cause hydronephrosis. It is diagnosed by ultrasonography, CT or MRI scans. Depending on the size of the renal calyces and renal pelvis observed, hydronephrosis is classified as mild, moderate and severe.

Calculi

Renal stone formation is mainly due to hypercalciuria. There is loss of calcium from the bones after SCI. In 8% of spinal cord injury patients, after 10 years following injury, upper tract calculi are found, most of them secondary to infection. Bladder calculi incidence in the first 9 months in patients performing intermittent catheterisation is 2.3%. The prevalence is higher in patients who are on indwelling catheter.(13)

Autonomic dysreflexia

Autonomic dysreflexia is characterised by paroxysmal hypertension, reflex bradycardia, increased sweating above the neurological level, headache and piloerection. It is seen usually in a spinal cord injury above T6 neurological level. Full bladder or over-distension of the bladder is a common cause of autonomic dysreflexia.(13)

MANAGEMENT OF NEUROGENIC BLADDER

Principle of neurogenic bladder management is to promote storage of urine, facilitate bladder emptying, while maintaining social continence.(29) This includes lifestyle modification, pharmacological and surgical interventions. Reducing detrusor overactivity and promoting bladder emptying by clean intermittent catheterisation (CIC) is the standard line of management in neurogenic bladder. It has several advantages and improves quality of life.(33)

Behavioural management

Timed voiding

Patients with overactive bladder producing urgency or reflex incontinence, timed voiding program can be taught. In this patients are instructed to urinate before the anticipated detrusor contraction. In patients with sphincter weakness this is useful as the incontinence is worse when the bladder is full. It is combined with restricting and monitoring the fluid intake and educating the patient about the relationship between the fluid intake and urine output.

Bladder stimulation

Stimulation of the bladder by stroking or pinching the perineal skin to cause reflex simulation has been tried but they are ineffective. Suprapubic tapping causes a mechanical stretch of the bladder wall and subsequent bladder contraction. Deeper

indentation of the bladder with a jabbing technique has been found to the most effective technique in controlled studies. It can be used by patients on condom catheters and patients with paraplegia who have good upper limb function.(34)

Valsalva and Credè's manoeuvre

Valsalva manoeuvre or straining can be used by patients with areflexic bladder or infrasacral lesion. Complete flaccidity of the pelvic floor can allow emptying by straining. The Credè's manoeuvre mechanically pushes out the urine from the bladder. Relaxed abdominal wall is a pre-requisite for Credè's manoeuvre. Credè's manoeuvre is reported to be superior to continuous bladder catheterisation in the long term.(35)

Anal stretch voiding

In paraplegics with spastic pelvic floor, effective voiding has been achieved by an anal stretch technique. It involves emptying the bladder by relaxing the pelvic floor by stretching the anal sphincter and performing the Valsalva manoeuvre.(13)

Urine collection devices

In tetraplegic patients, who are unable to perform self-catheterisation, and in whom any outflow obstruction is adequately treated, external condom catheter is the best tool for urine collection. If it is applied too tightly then it can lead to skin breakdown and urethral damage. Poor perineal hygiene can lead to recurrent UTIs.

Indwelling catheters are of two types – urethral or suprapubic. They are used if all other measure have failed or for patient convenience. Patients must be instructed about monthly catheter change, to take adequate amounts of fluids, control movements and to avoid traction on the catheter.

Adult diapers and other protective garments which contain high absorbency gel impregnated material can be used to keep the patient's perineal skin dry.

Clean Intermittent Catheterisation (CIC):

Neurogenic bladder leading to problems of bladder filling or emptying leading to urinary tract infection has been identified since the Greek times and it was a major cause of morbidity and mortality in spinal cord injury patients till clean intermittent catheterisation was described. CIC was first described by Teevan at around 1880 in patients with bladder dysfunction due to Syphilis in England where the patients were said to carry their catheters in theirs hat bands.

In the early 1950s Guttmann and colleagues described sterile intermittent catheterisation for acute spinal cord injury patients. All catheterisations on male patients were performed by a doctor assisted by a nurse or a trained catheter orderly. The women were catheterised by state registered nurses. In all cases, the non-touch technique with full aseptic precautions was used. This resulted in reduced urinary tract infections.(36) But this method did not gain popularity as it was a tedious job and had

to be done by a catheter team of Doctors or nurses and also due to shortage of manpower.

In 1970, Lapides and colleagues treated a woman who had neurogenic bladder secondary to multiple sclerosis with history of multiple urinary tract infection and was severely distressed as her social and sexual life had been turned upside down due to the urinary incontinence. They developed “clean intermittent catheterisation”, in which the catheter was not sterilised but only cleaned with antiseptic solution and catheterisation was done by the patient after washing her hands and not by using sterile gloves or forceps.(37)

The principle behind the “clean” intermittent catheterisation was that host resistance factors were adequate to check symptomatic urinary tract infection provided the bladder was emptied regularly and the bladder was not allowed to over stretch.(37)

The technique of self-catheterization was taught by the clinic supervisor. The patient washed her hands with soap and water, assumed a lithotomy position on the table, with her feet on the table and the knees held apart so as to expose the urethral meatus and introitus. A hand mirror was placed at the foot of the table so that the patient could visualize the urethral meatus when it was pointed out to her by the nurse. She was then given a catheter with some lubricant on the tip and instructed to insert the catheter through the urethral meatus into the bladder. Once she had drained the urine she was advised to remove the catheter slowly. She was advised to clean catheterisation every few hours to maintain continence. The insignificance of sterility was given by the same patient when she reported that once when her catheter fell down on the toilet floor and she did not have any antiseptic solution to sterilise the catheter she just continued with catheterisation and did not develop ill effects. This

finding revolutionised management of neurogenic bladder. Lapides and colleagues published numerous other articles regarding CIC which have formed the foundation of neurogenic bladder management.(37)

Even after 4 decades of this significant event, CIC remains the mainstay treatment of neurogenic bladder management worldwide.

Types of clean intermittent catheterisation:

1. "Clean Intermittent self Catheterisation" – In this type the patient himself does intermittent catheterisation to empty his bladder in regular intervals during day and night.
2. "Attendant Intermittent Catheterisation" – In patients who have lost hand functions due to any reason, a care-giver does the catheterisation intermittently.
3. "Sterile Intermittent Catheterisation" – It is performed by medical personnel in a sterile manner in acute or emergency conditions.(38)

Age is not a barrier for CIC. Children as young as 5 years can be taught to do CIC.(38) Attendant CIC is an alternative that can be taught to the patient's care taker, but in most of the situations it becomes socially unacceptable. Intelligent patient selection and enthusiasm from the patient to learn CIC are two of the most important pre-requisites to initiate CIC.

The advantages of CIC are:

1. Decreased incidence of urinary tract infections
2. Decreased incidences of renal and bladder calculi
3. Continence between catheterisations
4. Freedom from continuous catheterisation leads to increased satisfaction in sexual life in the patients and their partners.(39)

Clean intermittent catheterization is the safest bladder management method for spinal cord injured patients in terms of urological complications. Inappropriate selection of a bladder management method not only adversely affects patient quality of life, but also has a significant detrimental impact on the economic status of the health care system.(40)

Pharmacological management

Numerous drugs have been tried on persons with neurogenic bladder, those that inhibit detrusor activity are the most useful and effective.

Anticholinergic drugs

They are used to decrease detrusor overactivity. Propantheline bromide and hyoscyamine have been tried, but oxybutynin is the agent that is commonly used. Its dose ranges from 5mg once a day to four times a day. It is also available as a sustained release preparation. Patients with hepatic impairments require smaller doses. Oxybutinin solution can also be instilled in the bladder. Dry mouth and constipation are the most common side effects. Side effects are less when it is administered orally.(41) Oxybutinin is available as transdermal patch preparation but skin irritation limits its use. Tolterodine is a muscarinic receptor antagonist that can be used in patients with severe renal or hepatic impairment. It can be given at doses ranging from 1mg to 2mg twice daily. Darifenacin is newer muscarinic receptor antagonist, which is available as extended release tablet. It binds to M3 receptors and can be given at doses ranging from 7.5mg – 15mg. Trospium also can be given ata dose of 20mg twice daily

or as a sustained release preparation at 60mg once daily. Dry mouth, blurry vision and constipation are some of the major side effects.(42)

Adrenergic antagonists

They increase emptying in neurogenic voiding dysfunction. They include Alpha-1 adrenergic receptor antagonists like prazosin, terazosin and doxazosin. Tamsulosin is also used and it has fewer vascular effects and rarely causes hypotension.(43) All the above mentioned agents are effective in controlling the vascular manifestations of autonomics dysreflexia.

Adrenergic agonists

They increase the urethral resistance in patients with mild stress incontinence. In future, duloxetine (a serotonin and norepinephrine reuptake inhibitor) may be used to prolong the Alpha-adrenergic effects on the external urethral sphincter, which acts on the pudendal nucleus in the sacral cord.(44)

Estrogens

Estrogen application in post-menopausal women who have stress incontinence due to atrophy of urethral sub-mucosa, often restores or maintains the tissue and helps in incontinence.(45)

Muscle relaxants

Muscle relaxants like baclofen, tizanidine and dantroleum sodium are used to reduce spasticity. Their efficacy on reducing detrusor sphincter dyssynergia has never been observed. Intrathecal baclofen depresses the pelvic floor reflexes as well as the detrusor reflex. Hence it has limited value in managing an overactive bladder.(46)

Intravesical therapy

Botulinum A toxin can be used to decrease bladder hyperactivity. It can be injected to the bladder wall musculature at 30-40 sites for a maximum of 200 units, and it reduces detrusor overactivity for upto 6 months. Injection can be repeated after 6 months.(47)

Resinferatoxin can also be used for intravesical injections and has shown improvement in symptoms of overactive detrusor.(48)

Surgery

Surgical management of neurogenic bladder are of three types:

1. Bladder augmentation: It is recommended in patients with detrusor hyperactivity or reduced compliance which fails to respond to anticholinergic drugs. The principle is to create a low pressure reservoir. Patient should be counselled that he/she should be compliant with regular CIC even after the surgery. Long term complications are chronic bacteruria, possible risk of

neoplastic change, decreased intestinal transit time and malabsorption syndrome. It has a high level of patient satisfaction.(49)

2. Continent diversion: A continent catheterisable channel that opens into the abdominal wall is made using a section of the bowel to increase bladder capacity. Patients who are unable to do CIC because of strictures, false passages or fistulas are ideal for this procedure.(50) The intussuscepted small bowel, terminal ileum with the ileocecal valve, the appendix and a defunctional segment of the ureter can be used for this procedure. Sphincter related incontinence, if present will require closure.
3. Denervation procedure: Sectioning the sacral nerve roots or interrupting the peripheral nerve supply near the bladder, are some of the denervation procedures. Selective sacral rhizotomy is selectively identifying S3 nerve root that mediates the detrusor reflex and denervating it.(51) It results only in temporary areflexia. Over time, detrusor reflex reroutes through the other intact sacral roots. Bilateral S2, S3 and S4 denervation permanently abolishes sacral reflex but it also abolishes reflex erections and results in worsening of bowel problems.

   Peripheral denervation of the detrusor has been tried by transecting the detrusor above the trigone area of the bladder and resuturing it, by denervating the paravesical ganglia via a vaginal route, or the bladder has been over-distended to damage the intramural nerves and muscles. These methods have not gained popularity.(52)

Procedures to increase bladder contraction

Electrical stimulation

Attempts have been made to modulate detrusor contraction by implanting electrodes on the pelvic nerves, sacral roots, bladder wall and the conus. The electrodes are implanted on the anterior roots either intradurally or extradurally. Bilateral S2, S3, and S4 dorsal rhizotomies are performed, to prevent spontaneous hyperactive contractions. Super-selective rhizotomies, with modification of the stimulus parameters and electrode design are the future possibilities.(53)

Procedures to increase bladder outlet resistance

Urethral compression procedures are done for incontinence from decreased outlet resistance. They include injection therapy into the bladder neck and urethra to increase the bulk of the tissue under and around the bladder neck, an artificial sphincter or a fascial sling.(54) Electrical stimulation of pelvic floor muscles or nerves through rectal, vaginal or implanted electrodes is not effective.

Injection therapy

Teflon injections are given in the urethra for stress incontinence since years, but in recent years their use has declined due to danger of particle migration. Bovine collagen and autologous fat have also been used. There are potential side effects of these procedures and elderly and poor risk patients are ideally suited for the same.(55)

External compressive procedures

Fascial sling procedures which involve taking a 2cm strip of fascia from the anterior rectus abdominis fascia or tensor fascia lata. It is wrapped around the bladder neck

and attached anteriorly to the abdominal fascia or pubic tubercle. Pre-requisite for this procedure is to a have a low pressure and compliant bladder. Patients should be instructed about the need for lifelong CIC and inability to void with Valsalva or Crede methods after the procedure.

An artificial urethral sphincter, this consists of a cuff, a pressure regulating balloon, and a control pump. The cuff is implanted around the bladder neck. The pump is implanted in the labia or scrotum to allow the patient to open the cuff for voiding. Valsalva manoeuvre can be used and CIC is not compulsory after this procedure. Artificial sphincters have a significant impact on quality of life.(56)

Procedures to decrease outlet resistance

Sphincterotomy procedures are done in male patients who are unable to do CIC or refuse CIC. Condom catheters are ideal urine collection devices in such patients. Striated sphincter is usually ablated by incision. Prostatic resection is needed in older patients with prostatic obstruction. The long term results are compromised due to recurrent obstruction by stricture formation or dyssynergia.(57)

Urinary tract infection remains the most common complication of all the methods mentioned above used to manage neurogenic bladder in spinal cord injury patients.

Urinary tract infection (UTI):

Patients with neurogenic bladder are prone to repeated UTIs. A comparative study followed patients for 1 year was suggestive of increased episodes of bacteruria with fever were significantly more common in patients who followed attendant catheterisation than in patients on self-CIC or with indwelling catheters.(58)

Several studies have examined the value of prophylactic antibiotics for prevention of UTIs in SCI patients on CIC. The possible role of trimethoprim-sulfamethoxazole prophylaxis in patients with acute SCI in the first 4 months of CIC during bladder training was studied in a prospective randomized trial. There was significant reduction in bacteruria and symptomatic UTI in men in the antibiotic group compared with those on placebo. This difference was not observed in female patients.

But, adverse events related to antibiotic treatment and emergence of drug resistance were common and limit the usefulness of prophylactic antibiotics.(59)

Another study in patients with SCI-neurogenic bladder dysfunction conducted during initial management with CIC concluded that prophylactic antibiotics significantly reduced bacteruria but not clinical UTIs.(60) A meta-analysis examined the benefits and harms of antimicrobial prophylaxis for UTI in patients with SCI.(61) Results from 15 clinical trials were pooled and analysed and it suggested that there is no evidence to support the use of prophylactic antibiotics during CIC. In fact prophylaxis resulted in a two-fold increase in antimicrobial-resistant bacteria.(61) Appropriate use of antibiotics will reduce drug resistance. Spinal cord injury patients on CIC having recurrent clinical UTIs need to be treated repeatedly with antibiotics which may increase the incidence of multidrug-resistant bacteria.

Catheter associated urinary tract infection (UTI) is characterized by the new onset of symptoms accompanied by laboratory findings (bacteriuria, leukocyturia and positive urine culture) of a UTI.

The symptoms of UTI include: -

- Fever: Temperature more than 38 C. In presence of a fever, one should check for signs of sepsis.

Spinal cord injury patients, especially cervical and high thoracic lesions, are prone to poikilothermia (inability to regulate core body temperature). Urinary incontinence / failure of control or leaks around the catheter.

- Spasticity report on new or increased muscular hyper tonicity
- Malaise, lethargy or sense of unease: feeling tired or unwell, different from the person's usual state of health.
- Cloudy urine, report that the urine is not clear. There may be report of mucus or sediment.
- Malodorous urine a distinct change in urine odour, with a strong foul smell that persists on change of catheter equipment.
- Pyuria / leukocyturia presence of white blood cells generated by the mucosal lining and observed on urinalysis.
- Autonomic dysreflexia in individuals with spinal cord lesions at T6 and above, patients complain of feelings related to a sudden onset of elevated blood pressure and other symptoms such as headache, sweating, flushing brought on by a noxious stimuli, such as bladder distension/bladder infection.(62)

Treatment of UTI in patients with SCI is based more on personal experience of the treating physicians than on evidence. This may be due to the unavailability of evidence-based data. Excessive treatment with antibiotics will lead to development of multi-resistant organisms. Therefore antibiotics should be used judiciously. There is a need for early detection and treatment of urinary tract infections to decrease morbidity and subsequent complications.

C-REACTIVE PROTEIN:

C-reactive protein (CRP) is one of the blood tests used to assess, diagnose, and inflammation. The role played by CRP in physiological processes is not clear. CRP was the first acute-phase protein to be described, and is a sensitive marker of inflammation and tissue damage.(63) (64) Precise response and ease of measurement, make CRP an ideal marker of inflammation.

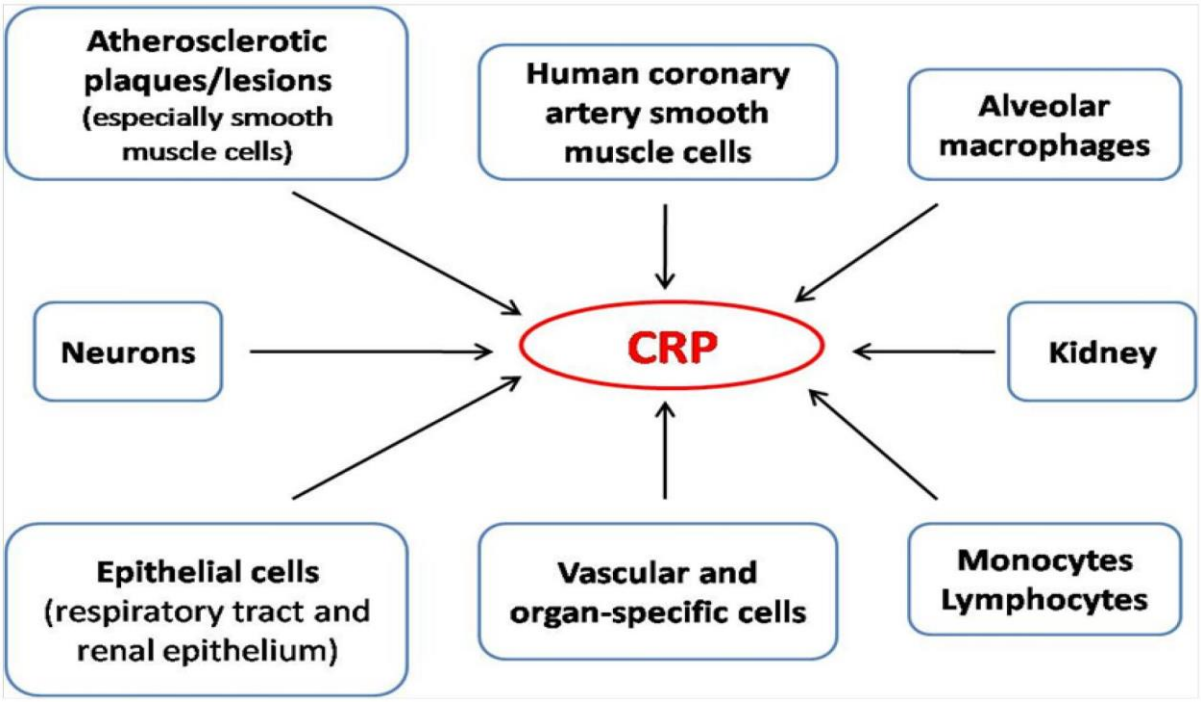
CRP was discovered in 1930 by William Tillett and Thomas Francis of Rockefeller University.(65) A third serologic fraction or 'fraction C' isolated from pneumococcus infected patients, was different from capsular polysaccharide.(65) Oswald Avery and Maclyn McCarty, described that CRP as an 'acute-phase reactant' that was found to be increased in serum of patients having a spectrum of inflammatory stimuli.(66, 67) CRP was found to have the function of conjugating pathogens and inducing their destruction by complement system. It was also studied as a screening marker of inflammation, disease activity, and as a diagnostic adjunct.(68)

C-reactive protein (CRP) is an annular (ring-shaped), pentameric protein found in blood plasma, whose levels rise in response to inflammation. It, belongs to pentraxin family of proteins which shows a 1000-fold or more increase in concentration during the occurrence of an injury, inflammation or tissue death.(69) The plasma half-life of CRP is about 19 hours and it is constant under all conditions of health and disease. (63,70) It is an acute-phase protein of hepatic origin that increases following interleukin-6 secretion by macrophages and T cells. Its physiological role is to bind to lysophosphatidylcholine expressed on the surface of dead or dying cells (and some types of bacteria) in order to activate the complement system via the C1Q complex.(71)

This acute phase response occurs as a result of a rise in the concentration of IL-6, which is produced by macrophages as well as adipocytes in response to a wide range of acute and chronic inflammatory conditions such as bacterial, viral, fungal infections, rheumatic and other inflammatory diseases, malignancy and tissue injury and necrosis. These conditions cause release of interleukin-6 and other cytokines that trigger the synthesis of CRP and fibrinogen by the liver. (69) C-reactive protein is also produced by the atherosclerotic lesions (especially by smooth muscle cells and macrophages), kidneys, neurons, and alveolar macrophages.(72)

Normal concentration in healthy human serum is between 5 and 10 mg/L, increasing with ageing. (73) Higher levels are found in late pregnant women, mild inflammation and viral infections (10–40 mg/L), active inflammation, bacterial infection (40–200 mg/L), severe bacterial infections and burns (>200 mg/L).(68)

Figure 4: Extra hepatic sites of CRP production



Source: Chanre journals

Role of CRP in physiology and pathology

CRP, is a biomarker of inflammation, and is also a direct contributor in atherosclerosis as it functions both as 'pro-inflammatory' and 'anti-inflammatory' molecule.(69) With the availability of high-sensitivity assays for determining CRP, it is one of the independent predictors of cardiovascular disease. CRP level, elevates in acute coronary syndromes, has a prognostic value in patients with cardiovascular complications and in apparently healthy individuals. The *in vivo* mechanisms of CRP as a mediator of the inflammatory state and thrombotic complications are continuing to be studied.

CRP as a marker of diseases

In the absence of inflammation, CRP is not elevated. Chronic microbial infections, smoking, BMI, coffee consumption, oral contraceptive use, and genetics influence the baseline concentrations of CRP.(74) Though the rise in CRP is non-specific, the amount of rise and the pattern of rise will help deduce the diagnosis.

CRP during normal pregnancy

CRP will be useful in diagnosing infections in new-borns as it does not cross the placental barrier.(75) Amniotic fluid and fetal urine contain CRP, and its elevated levels are associated with adverse pregnancy outcome.(75) Human placenta produces and releases CRP, like other placental proteins, mainly into the maternal circulation.

CRP and cardiovascular risk

CRP and cardiovascular risk association is predominantly by systemic inflammation. CRP mostly does not contribute directly to cardiovascular disease as a pathogenic factor. Using widely available high-sensitivity assays, CRP levels of 1, 1 to 3, and 3 mg/L have been classified respectively as low, moderate, and high-risk groups for future cardiovascular events. Individuals with LDL cholesterol below 130 mg/dL and CRP levels of 3 mg/dL represent a high-risk group.(70,76)

CRP and cancer

CRP levels have been used to predict the risk of cancer, detect cancer recurrence, and in prognosis.(75) It is a biomarker of inflammation and indicator of the immune response to tumor.(77) Its role as a predictor of survival has been shown in multiple myeloma, melanoma, lymphoma, ovarian, renal, pancreatic, and gastrointestinal tumors.(78) There is evidence to suggest that, there is elevation of CRP with the progression of melanoma, ovarian, colorectal and lung cancers, and recurrence of cancer after surgery.(78,79)

CRP and infection

CRP is an important factor in determining the etiology of infection. CRP levels can be significantly higher in bacterial infections. A value higher than 100mg/L strongly suggests bacterial infections, whereas that below 10 mg/L indicates viral infection.(80) Simultaneous determination of procalcitonin can add specificity in the case of bacterial infections.(81) CRP is also helpful to distinguish infection from an autoimmune flare.(82)

CRP is a more sensitive and accurate reflection of the acute phase response than the ESR (Erythrocyte Sedimentation Rate).(83) ESR may be normal while CRP is elevated. CRP returns to normal more quickly than ESR in response to therapy. Several studies investigated differential diagnostic values of CRP in a series of inflammatory disease (including inflammatory bowel disease, Intestinal Lymphoma, Intestinal Tuberculosis and Behcet's Syndrome), and compared CRP to other inflammatory biomarkers, such as ESR and WBC.(83)

CRP and inflammatory diseases

In inflammatory diseases, CRP level represents the disease activity. There is a direct correlation of CRP with RA and inflammatory bowel diseases like Crohn's disease.(84,85) In contrast, in conditions like SLE, CRP is not significantly elevated.

CRP and obesity

In obese individuals who are insulin resistant, and are in line with the weight loss-associated improvements in insulin resistance, CRP concentrations are elevated. The relation between CRP concentrations and insulin resistance is independent of obesity.(86)

CRP and diabetes

Elevated levels of CRP and IL-6 predict the development of type 2 diabetes. This association supports a possible role for inflammation in diabetogenesis. CRP is a powerful independent predictor of diabetes, after adjustment for obesity, clinical risk factors, and fasting insulin levels.(87) Minor increase in CRP level has also been reported to be associated with a number of medical conditions that do not appear to be associated with inflammation. Elevated CRP is also observed with several genetic polymorphisms of the CRP and other genes, ethnicity, dietary patterns and obesity.(69)

CRP and Spinal cord injury

A similar study which assessed the usefulness of serial concentration of C-reactive protein, as an indicator of urinary tract infection in patients with spinal cord injury concluded that treatment with antibacterial drugs to which the bacteria were fully sensitive resulted in a rapid decrease of the CRP values, and very low or trace amounts were attained within a week. Patients ineffectively treated or reinfected showed increasing or slowly decreasing CRP values. Their results from patients with spinal cord injury also indicated that serial measurements of CRP would be useful in indicating a successful response to treatment for those with symptomatic UTI.(88)

Values of serial CRP concentrations were assessed in patients with spinal cord injury as invasive urinary tract infection can be difficult to diagnose in spinal cord injury patients due to absence of classical symptoms of urinary tract infection. Successful treatment of UTI was associated with a fall in CRP to normal. Increased values of CRP were also shown in patients who did not have clinical UTI or other sites of sepsis but who were bacteriuric-presumably, the cause of this raised CRP concentration was inflammation within the urinary tract. An increased concentration of CRP is unequivocal evidence of an active tissue damaging process, but values should be interpreted in the light of full clinical information. Increased value of CRP in the presence of bacteriuria and the absence of other known sites of sepsis or inflammation indicates an invasive urinary tract infection, and as such requires treatment with antibiotics. Conversely, a normal value of CRP in the presence of bacteriuria indicates simple bladder colonisation and does not require antibiotics. Serial monitoring of CRP may therefore be helpful in distinguishing infection from colonisation and in monitoring the response of UTI to treatment.(88)

Justification for the current study

In persons with spinal cord injury, neurogenic bladder is a common occurrence and they are placed on indwelling per urethral catheters or are taught self intermittent clean catheterisation for bladder drainage. However this brings with it a complication of urinary tract infection, which is a major contributor to significant morbidity in these patients.(89) The physiology of persons with spinal cord injury change post injury, there are no classical symptoms of burning micturition, pain abdomen or fever as compared to the normal population in urinary tract infection. Only a general feeling of being unwell, urine leaks, cloudy urine, foul smelling urine, increase in spasticity or autonomic dysreflexia in persons with a neurological level above T6 point to an on-going urinary tract infection.(62) Hence, physicians rely on their clinical suspicion and physical examination findings to make a provisional diagnosis and treat it. However in case of continued course of being unwell, a review of the parameters is made and treatment is changed accordingly. This often results in increased number hospital admission days, treatment cost and significant emotional trauma to the patient. It is the need of the hour to have an objective measure to assist in predicting urinary tract infection and the response to treatment. In this study C-reactive protein has been selected, as it is a more sensitive and accurate reflection of the acute phase response than the ESR (Erythrocyte Sedimentation Rate). CRP also returns to normal more quickly than ESR and TC (Total white blood cell counts) in response to therapy.(83), and is therefore more indicative of response to treatment.

Methodology

Setting

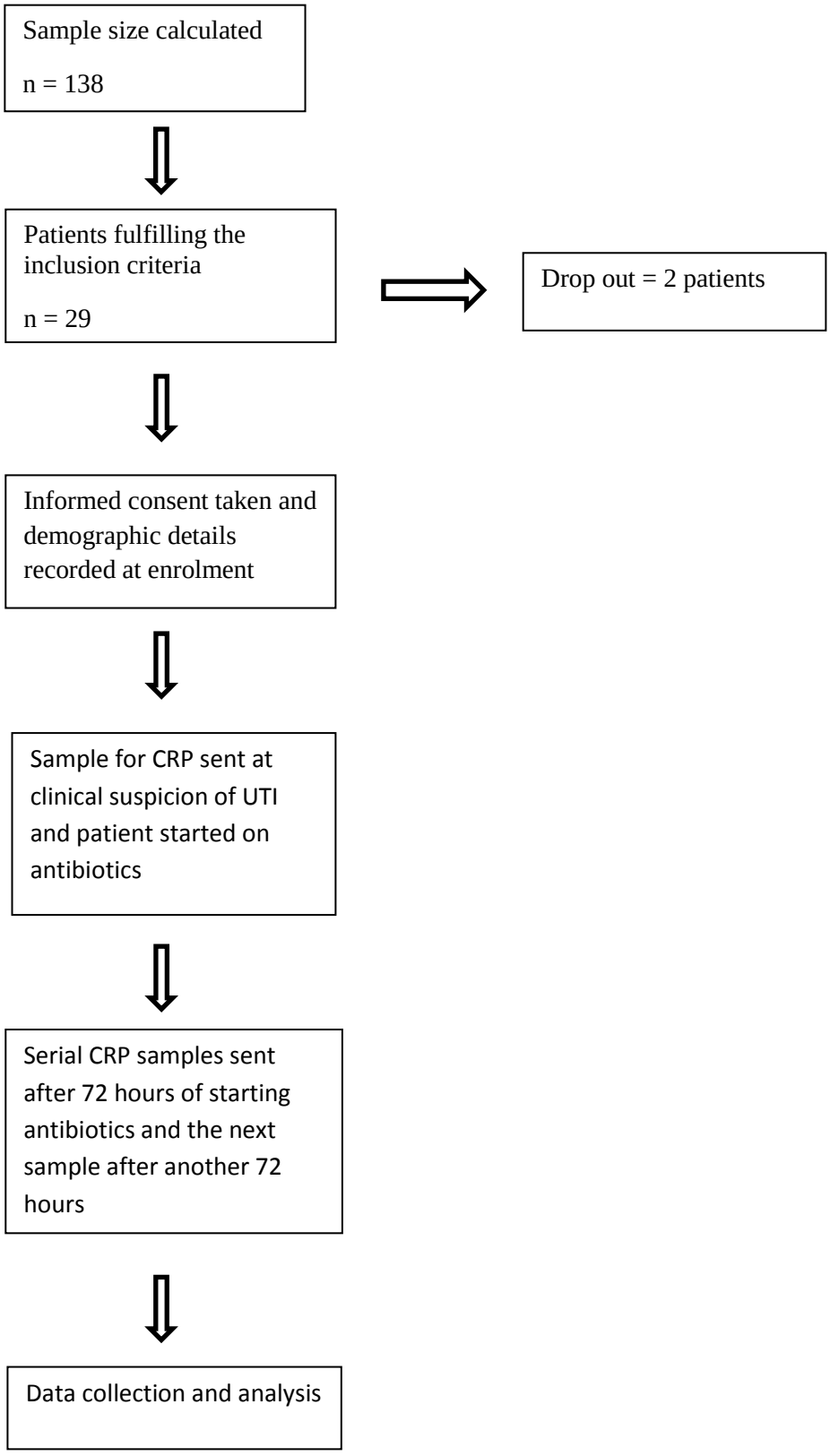
The present study was done in Christian Medical College, Vellore, situated in the state of Tamil Nadu, India. It is a tertiary care hospital with 2500 inpatient beds, and average out patient census of about 5000 patients per day. The Department of Physical Medicine and Rehabilitation in CMC, has 123 inpatient beds and an average of 100 outpatients per day. Every year, about 300-500 patients with SCI are referred here for rehabilitation. On an average about 80-100 patients receive inpatient care in a year, which includes surgical and medical management of complications arising from SCI.

The study

This was a prospective observational study. The present study was approved by the Institutional Review Board of the Christian Medical College. 29 patients who fulfilled the inclusion criteria were recruited for the study after obtaining informed consent. Demographic details including name, age, sex, address, socio-economic back-ground, details of injury, past medical history details were collected from the patient and medical records.

At the time of admission as standard of care, sample for urine culture, blood sample for total counts, differential counts was sent. They were followed through the course of their admission. Thereafter, as per department protocol, for persons who were yet to be taught self clean intermittent catheterisation and were on indwelling urethral catheters, urethral catheters were changed every week .

Flowchart of the study:



Current protocol for treatment of UTI in the Department of PMR, CMC, Vellore

The current protocol in the department is to start treatment when there is clinical suspicion of UTI suggested, by the patient complaining of generalized feeling of being unwell, fever (>38 C), increased urine leaks between clean intermittent catheterisation, increase in spasticity, cloudy, foul smelling urine, and by clinical examination of the patient. Once there is clinical suspicion of UTI, blood is taken for total and differential counts and a urine sample for culture and sensitivity is sent. The patient is then started on antibiotics based on the culture and sensitivity taken at the time of admission and the patient is followed up. If the signs and symptoms respond to treatment then the antibiotic course is completed. If they do not subside then the patient is started on the antibiotic based on the culture and sensitivity taken just before starting the treatment.

In this study, at clinical suspicion of urinary tract infection, a blood sample for CRP was taken before starting treatment, 72 hours after starting the treatment and the next sample was taken 72 hours later i.e. on day zero, day three and day seven. Total counts were sent as per the standard protocol of the department which were also recorded.

• Urinary tract infection* was suspected if there was

Fever (>38°C) – more than 2 episodes and associated with -

– Urine leaks

– Increase in spasticity or autonomic dysreflexia in persons with lesions above neurological level of T6.

– Malaise and generalized feeling of not being well

– Purulent, turbid or bad smelling urine

– Presence of significant bacteriuria as defined by more than 10^5 CFU in a sterile catheter sample.

* As per Catheter associated urinary tract infection (CAUTI), CDC guidelines -2014

C-reactive protein levels were identified using standardized laser nephelometry method. Normal range of C-reactive protein was taken as less than 6 mg/L.

Urine culture:

The urine specimen for culture was collected from an indwelling catheter by direct puncture of the proximal portion of the catheter after disinfecting the tube.

The specimen was sent directly to the lab and maintained at 4°C prior to processing for culture. A maximum transport time of 2 hours was maintained.

The routine urine culture was performed by the semi-quantitative culture method.(90) An initial assessment of the un-centrifuged specimen gram stain was performed to grade the specimen for the amount of inflammatory reactive cells, epithelial cells and bacteria.(91) The semi-quantitative culture was performed with 10µl of the specimen on sterile and quality passed 7% Sheep blood agar and Mac Conkey media, prepared in the Department of Clinical Microbiology.(90,92) The cultures were incubated aerobically at 37°C for up to 48 hours.

Culture interpretation is done using the following criteria:

1. Amount of inflammatory response as seen on gram stained smears of the urine specimen.
2. The concomitant symptoms at the time of culture
3. The growth in culture.

Culture growth	**Interpretation**(93)
< 1000 colony forming units (cfu)/ ml single organism	Insignificant bacteriuria
1000- 100,000 CFU/ ml unto 2 organisms	Probably significant bacteriuria
>100,000 CFU/ml unto 2 organisms	Significant bacteriuria
More than 3 pathogens in culture in probably significant / significant counts	Mixture of organisms
Normal flora	Contaminants, Insignificant

Further, the gram negative bacilli are identified using the oxidase test and the preliminary screening media consisting of the mannitol motility media, triple sugar iron agar, peptone water, Simmon's citrate and Christensen's urea media. Enterococcus species is identified using bile esculin agar.

Susceptibility testing is performed by the Kirby-Bauer disk diffusion method on Mueller-Hinton agar, Difco, India. Standard American Type culture collection (ATCC) control strains were used as quality control strains for the drugs tested.

Inclusion criteria

1. Age between 18 years to 60 years, irrespective of sex, mode of injury, who can speak or understand Tamil, English and Hindi.
2. On indwelling urethral catheter or self intermittent clean catheterisation for bladder drainage.
3. Period of injury, more than 3 weeks.
4. Informed consent given by the patient to participate in the study.

Exclusion Criteria:

1. Injury less than 3 weeks.

2. Undergone any surgical procedure within 3 weeks

3. Pressure sore, more than grade 2

4. History of inflammatory disorders – Rheumatoid arthritis, seronegative spondyloarthropathy, inflammatory bowel disease

5. Patients on tracheostomy

6. Infection due to causes other than urinary tract infection

7. Anaemia with haemoglobin less than 8 g/dl

Outcome variables

1. Serial concentration levels of C-reactive protein
2. Serial concentration levels of Total WBC counts
3. Presence or absence of fever reported as
    i. ‘Yes’ if fever was present
    ii. ‘No’ if fever was absent

Sample size calculation

By assuming 90% sensitivity and specificity of C-reactive protein with 5% precision and 95% confidence interval, the required sample size would be 138.

Formula

$$n = \frac{Z^2_{1-\alpha/2} p(1-p)}{d^2}$$

Where,

p : Expected proportion

d : Absolute precision

1- α/2 : Desired Confidence level

Statistical methods:

Data was entered in excel format and screened for outliers and extreme values using Box-Cox plot and histogram (for shape of the distribution). Summary statistics used for reporting demographic and clinical characteristics. Mann-Whitney U test for data with non-normal distribution with Fever. Differences considered significant at $p<0.05$. All the statistical analysis was performed using SPSS 18.0. Pearson's co-relation test was applied to test for co-relation between variables.

Results

29 patients, all males, who fulfilled the inclusion criteria, were recruited between April 2016 and June 2017. They were followed up during their course of their admission and on clinical suspicion of UTI, serial CRP measurements were done as described earlier. Total counts levels were also recorded and fever was recorded as 'Yes' if fever was present and 'No' if fever was absent. Two patients dropped out, one due to medical complications and one got discharged at request, and they were not included for analysis.

All the patients had significant bacteruria in urine culture and UTI was diagnosed based on CDC 2014 guidelines. 26 patients received urine culture sensitivity appropriate antibiotics. Total WBC counts recording were available only for 20 patients.

Out of the 27 patients, 17 patients were on indwelling urethral catheter for bladder management and 10 were performing clean intermittent catheterisation as shown in the table below.

Table no. 4: Patients and bladder drainage method

Bladder drainage method	No. of patients
Indwelling urethral catheter	17
Clean intermittent catheterisation	10

Table no. 5: No. of patients with and without fever

Day	No. of patients with fever	No. patients without fever
Day 0	27	None
Day 3	13	14
Day 7	None	27

Table five shows that out of the total 27 patients in the study, all the patients had fever on day zero, 13 patients had fever on day three and none had fever on day seven.

Table no. 6: Mean and SD of CRP with time

Day	Mean	Standard deviation(SD)	p-value in relation with Day 0
Day 0	93.17	50.15	-
Day 3	58.87	49.94	0.001
Day 7	16.46	11.64	<=0.001

Table six shows that mean value of CRP on day zero was 93.17 (SD 50.15). On day three, mean value of CRP was 58.87 (SD 49.94) and on day seven mean value of CRP was 16.46 (SD 11.64). p-value of CRP on day three when compared with day zero was 0.001 and of day seven with day zero was less than or equal to 0.001, which indicate that the fall of CRP levels where significant.

Figure 5: Relationship between CRP and time

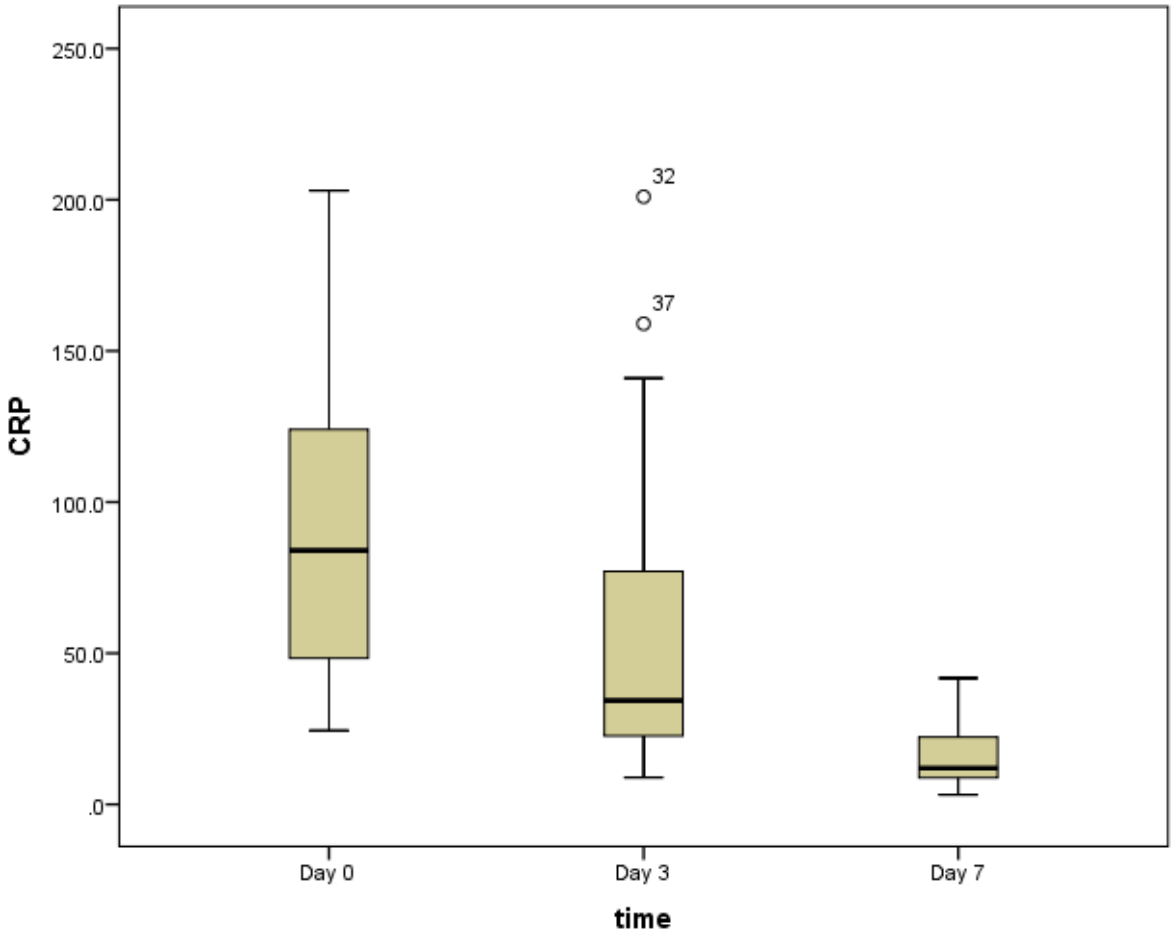


Table no.7: Mean and SD of total WBC counts with time

Day	Mean	Standard deviation(SD)
Day 0	14413.04	5242.42
Day 3	7423.81	2093.30
Day 7	7500.00	1815.72

Table seven shows that mean value of total WBC counts on day zero was 14413.04 (SD 5242.42). On day three, mean value of total WBC counts was 7423.81 (2091.30) and on day seven, mean value of total WBC counts was 7500 (SD 1815.72).

Figure 6: Relationship between Total WBC counts and time

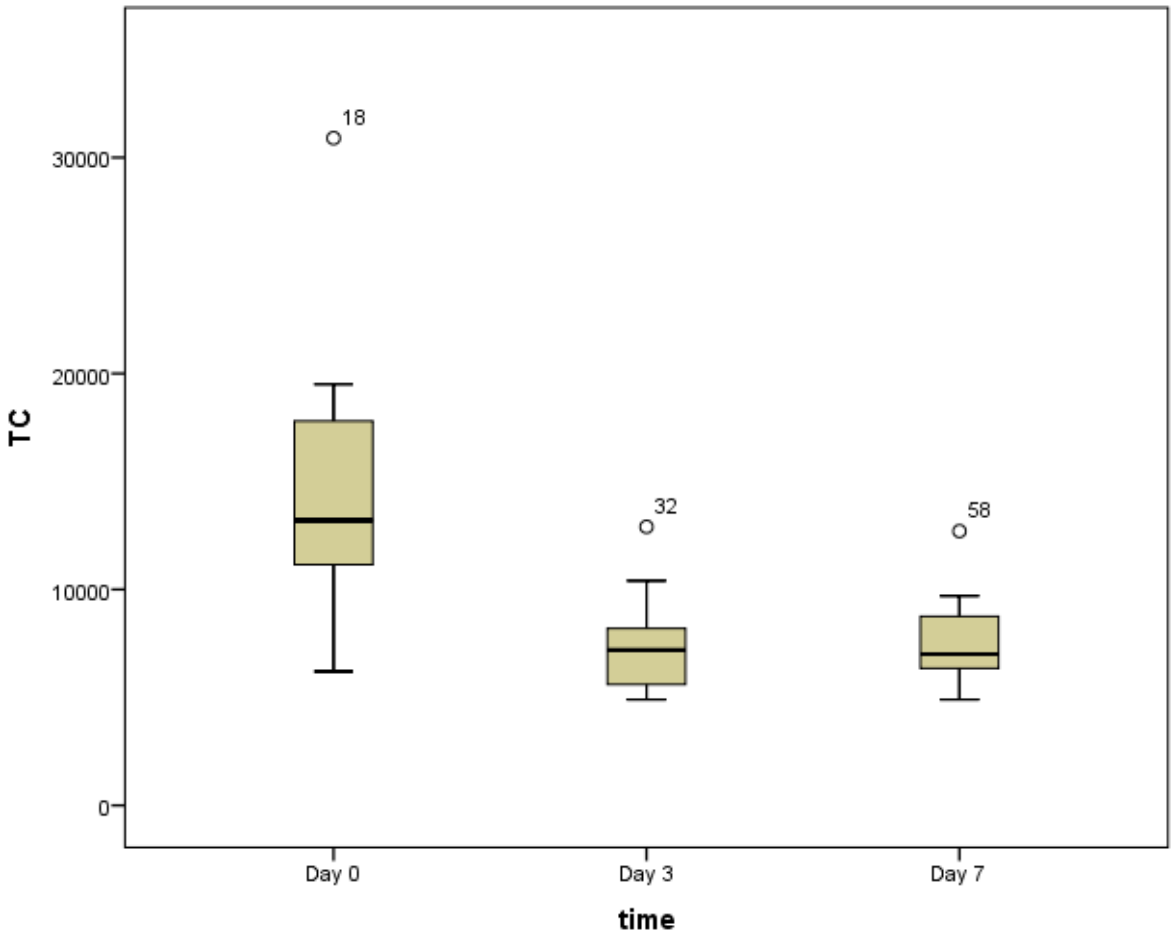


Table no.8: Mean and SD of CRP with and without fever

CRP value	Fever present	Fever absent
Mean	88.48	24.64
Standard deviation	51.76	25.73

Table eight shows that mean value of CRP during presence of fever was 88.48 (SD 51.76).

Figure 7: Relationship between CRP and fever

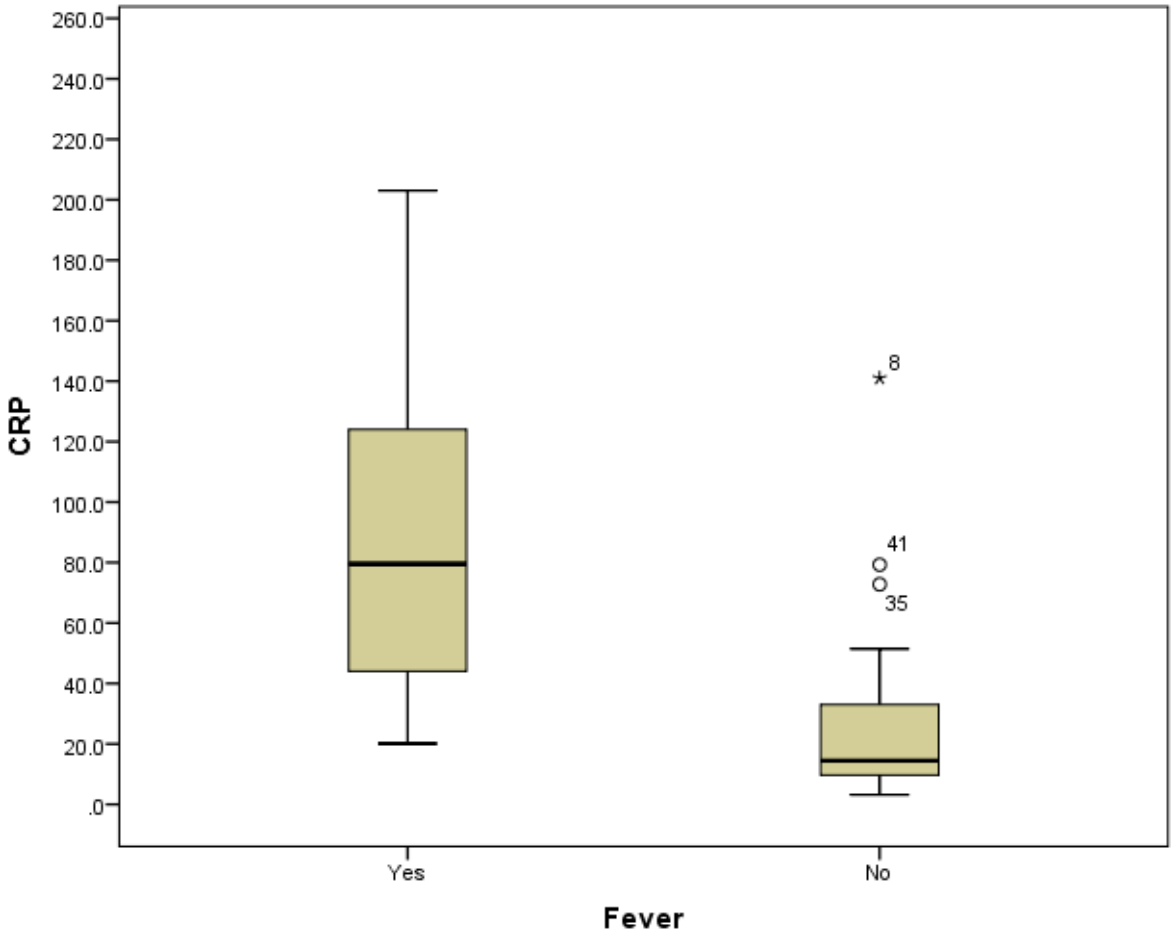


Table no.9: Mean and SD of Total WBC counts with and without fever

Total counts	Fever present	Fever absent
Mean	12424.24	7335.48
Standard deviation	5491.30	1714.94

Table nine shows that mean value of Total counts during the presence of fever was 12424.24 (SD 5491.30) and mean value of Total counts during the absence of fever was 7335.48 (SD 714.9).

Figure 8: Relationship between Total WBC counts and fever

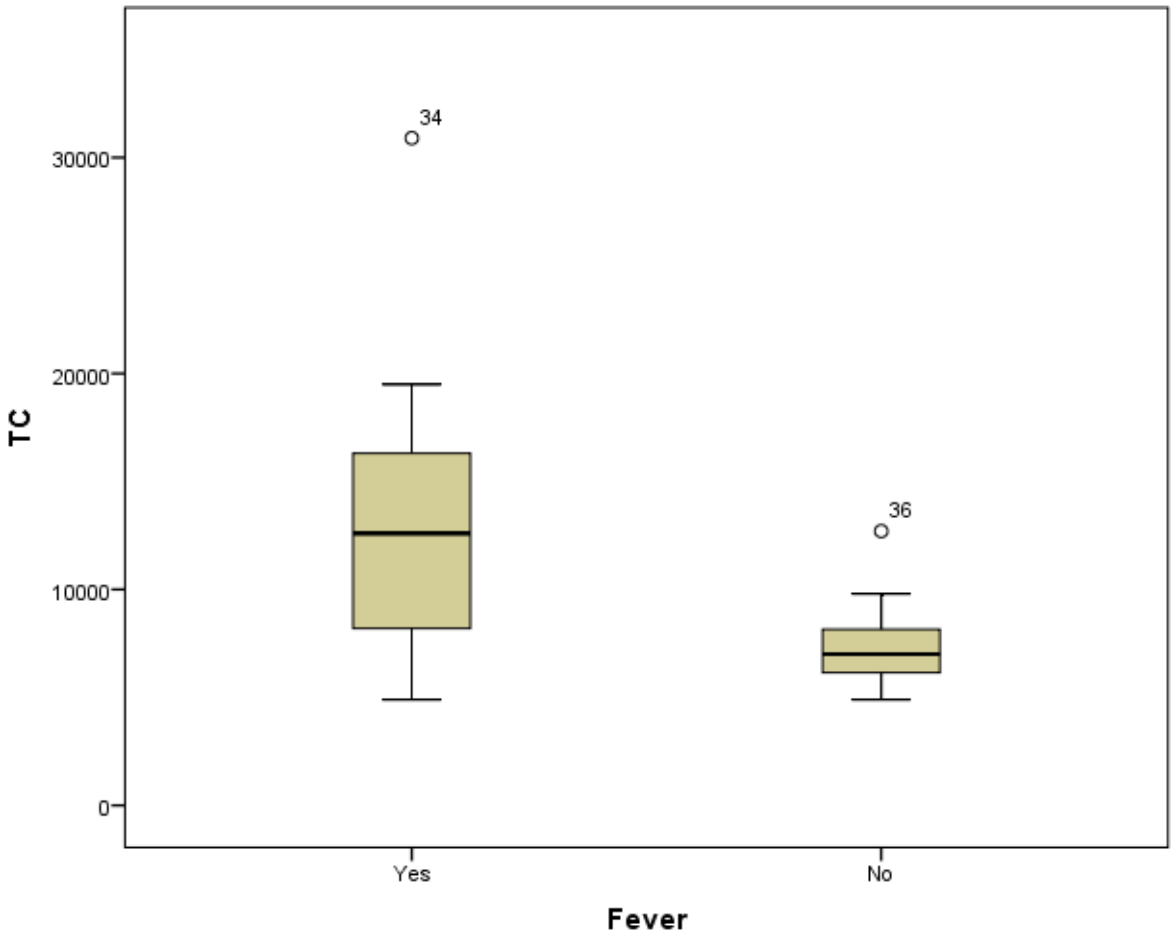


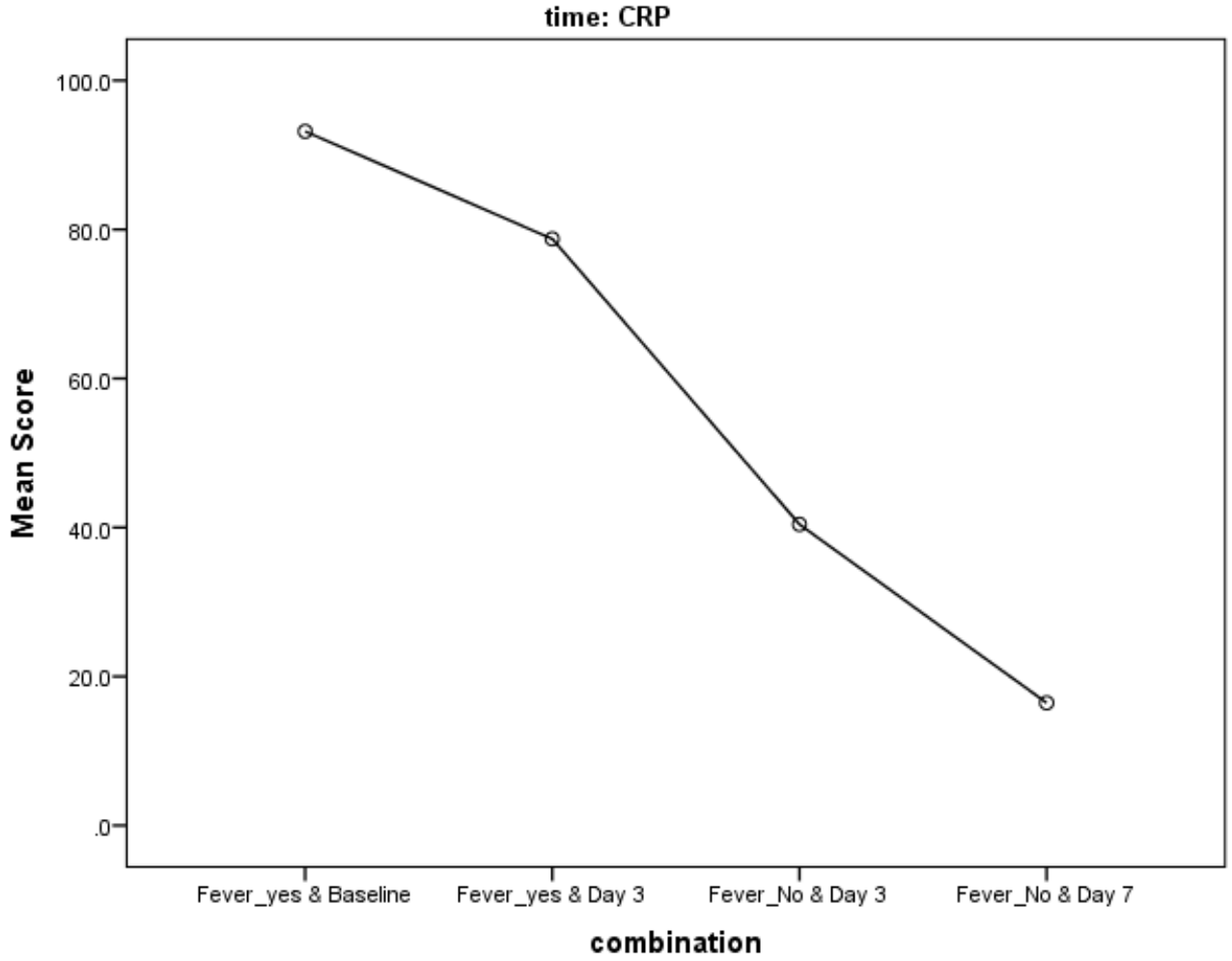
Figure eight is a box-cox plot which shows the relationship of total WBC counts with fever.

Table no.10: Mean and SD of CRP and total WBC counts with and without fever

Day	CRP		Total WBC counts	
	Mean	**SD**	**Mean**	**SD**
Day 0 with fever	93.17	50.15	14413.04	5242.42
Day 3 with fever	78.73	55.74	7850.00	2584.24
Day 3 without fever	40.42	36.86	7036.36	1551.30
Day 7 without fever	16.46	11.64	7500.00	1815.72

Table 10 shows that mean value of CRP on day zero, with fever was 93.17 (SD 50.15) and that of total WBC counts was 14413.04 (SD 5242.42). On day three with fever, mean value of CRP was 78.738 (SD 55.74) and that of total WBC counts was 7850 (SD 2584.24). On day three without fever, mean value of CRP was 40.42 (SD 36.86) and that of Total WBC counts was 7036.36 (SD 1551.30). Mean value of CRP on Day seven without fever was 16.46 (SD 11.64) and that of Total WBC counts was 7500 (SD 1815.72).

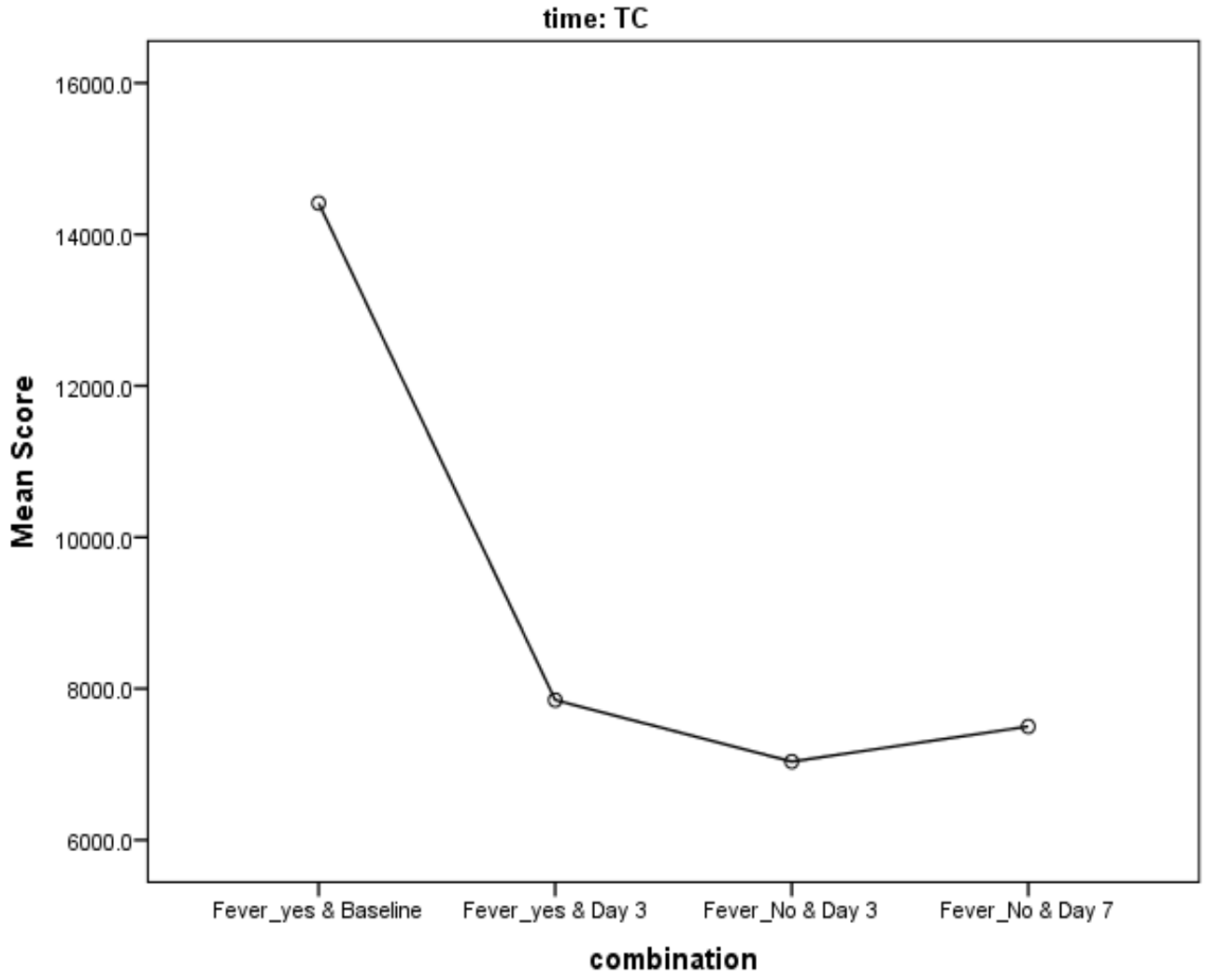
Figure 9: Relationship of CRP and presence and absence of fever



*Baseline = Day 0

Figure nine is a line diagram which shows the relationship of CRP and fever. There is a linear fall in the CRP levels with time and the CRP levels are elevated in patients without fever indicating a persistent on-going inflammation.

Figure 10: Relationship between Total WBC counts and presence and absence of fever



*Baseline = Day 0

Figure 10 is a line diagram which shows the relationship of total WBC counts with fever. The fall in total WBC counts is in a non-linear fashion and the total WBC counts are within the normal range even in patients who are febrile.

Table no.11: Bacterial profile in the urine culture

No. of patients	Bacterial species
18	E.coli sp.
4	Klebsiella sp.
3	Mixture of organisms
1	Pseudomonas sp.
1	Enterobacter sp.

Table 11 shows, urine culture of 18 patients grew E.coli species, out of which seven patients had another organism growing with E.coli. Four patients grew Klebsiella species in their urine culture, three patients grew a mixture of organisms, and one each grew Pesudomonas species and Enterococcus species respectively.

Table no.12: Co-relation between CRP and Total WBC counts

Day	CRP and Total WBC counts	
	R- value	p-value
Day 0	0.401	0.052
Day 3	0.422	0.056
Day 7	0.138	0.561

Co-relation of CRP and total WBC counts (Pearson's co-relation) shows that on day zero, R-value was 0.401, p value was 0.052. On day three, R-value was 0.422 and p value was 0.056. On day seven, R-value was 0.138 and p value was 0.561.

Figure 11: Co-relation of CRP and Total WBC counts on day 0

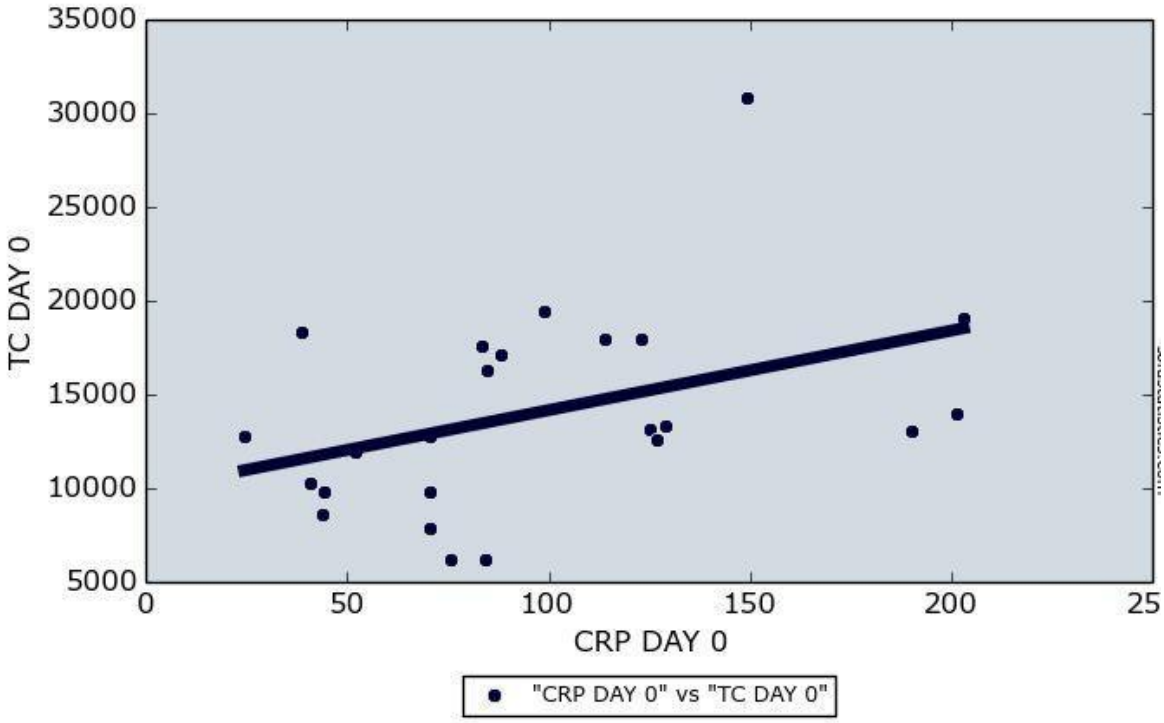


Figure 12: Co-relation of CRP and Total WBC counts on day 3

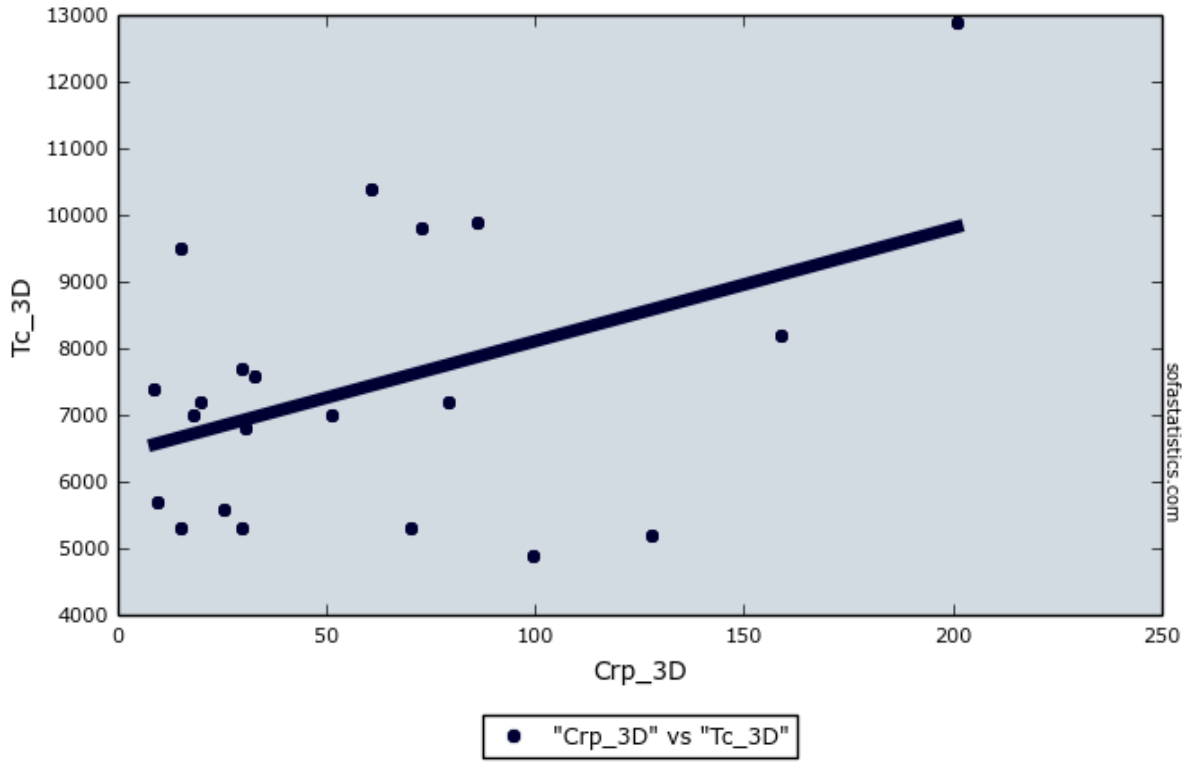
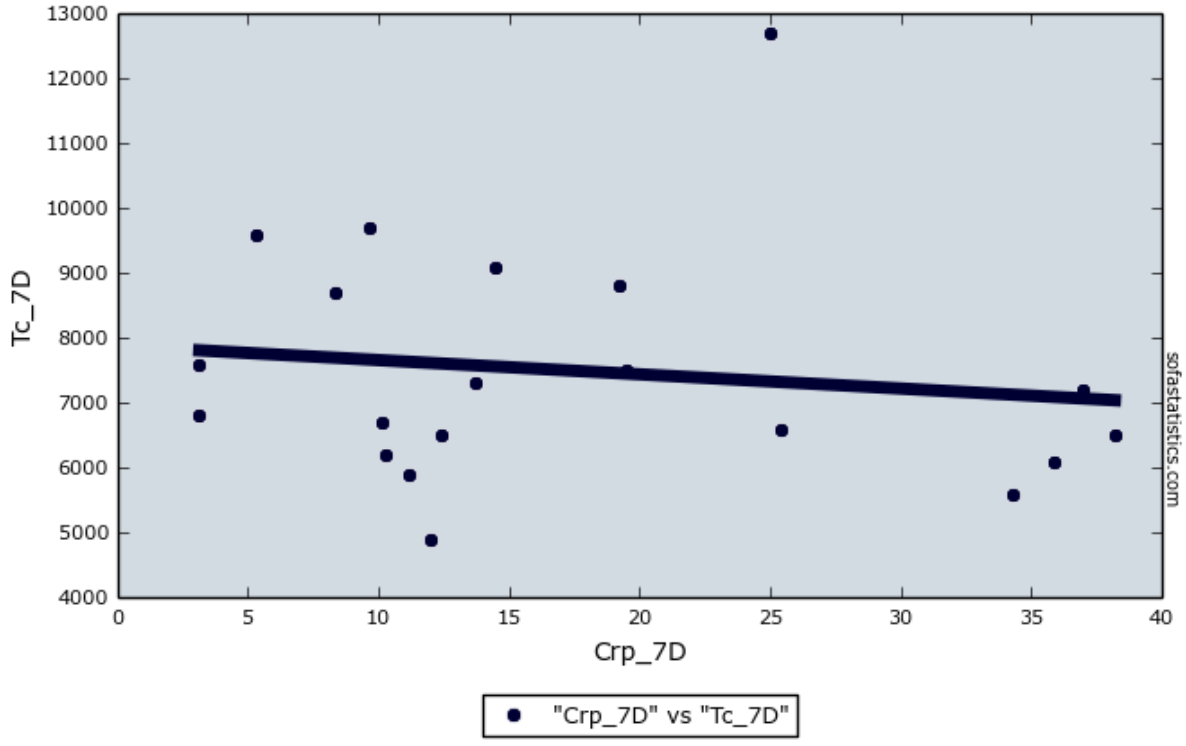


Figure 13: Co-relation of CRP and Total WBC counts on day 7



Discussion:

Spinal cord injury leads to a lot of secondary complications, which, if not managed appropriately, cause significant morbidity and mortality. Neurogenic bladder is seen in almost all the spinal cord injury patients. Urinary tract infection is the most common complication of neurogenic bladder, which if not identified early and appropriately treated, leads to further morbidity and mortality. In the early 1900s, UTI was one of the leading causes of morbidity and mortality in spinal cord injury patients.(8) Better understanding and improved treatment measures of neurogenic bladder and urinary tract infection, has significantly reduced the complications and has contributed in improving the active and productive life of spinal cord injury patients.

The present study was conducted with the objectives to see if C-reactive protein can be used as a surrogate marker for detecting urinary tract infection in persons with SCI and if it can be used to assess response to treatment. 29 patients were recruited for the study. Two patients dropped out of the study and were not taken for analysis. Out of the 27 patients, 17 were on indwelling urethral catheters and 10 were performing clean intermittent catheterisation for bladder management. All the patients were males aged between 18 years to 65 years.

In the study CRP was measured in mg/L and normal range was taken as serum level less than 6 mg/L. Total WBC counts was measured in cells/cubic mm and normal range was considered between 4000-12000 cells/cubic mm.

Presence of fever was a criterion for suspecting of UTI; hence all the patients had fever on day zero. On day three, 13 patients had fever and none had fever on day seven.

C- reactive protein levels were elevated on day zero in all the patients, mean and standard deviation was 93.17(50.15), indicating of an on-going inflammatory process. A CRP value higher than 100mg/L strongly suggests bacterial infections.(80) It was attributed to UTI, based on the clinical examination and the symptoms as reported by the patient, and after excluding all other possible causes of inflammation and UTI was confirmed by presence of significant bacteruria in the urine culture and after applying the CDC 2014 guidelines. Patients were started on appropriate antibiotics based on the urine culture sensitivity report. Three days later, 13 patients were febrile and 14 patients were afebrile. CRP levels decreased in all the patients, but remained elevated above the normal range, with a mean and SD of 58.87(49.94). This indicated that there was positive response to treatment, but active inflammation was still persistent. On day seven, all the patients were afebrile and CRP values of all the patients decreased further in a linear fashion and almost attained the normative range, mean and SD being 16.46(11.64).

The linear fall in CRP levels with the treatment was suggestive of an appropriate reflection of response to treatment. (88)

As Total WBC counts are done to track the response to treatment in the standard treatment protocol, their values were recorded and was analysed. Values for all the three time periods were available for 20 patients. The total WBC counts on day zero was elevated for all the patients, with the mean and SD being 14413.04 (5242.42).

On day three, total WBC counts showed a fall in their levels, with mean and SD being 7423.81(2093.30). An interesting point that was observed was that, the total WBC counts had fallen down to its normal range (Normal range being 7000-11,000) even in patients who had fever on day three. On day seven, when none of the patients had fever the mean and SD of total counts was 7500 (1815.72). The mean of total WBC counts on day three and day seven were similar and within the normal range. This is suggestive that even though the total WBC counts had reached its normal range, the inflammatory process in this study being UTI, continued and total WBC counts did not exactly reflect the response to treatment.

Pearson's co-relation test was used to test the co-relation between CRP and Total WBC counts. A p-value is obtained, which is significant if the value is less than 0.05 and an R value is obtained, significance of which is mentioned in the table below.

Table no.12: Significance of R-value

Value	Co-relation
One	Positive co-relation
Zero	No co-relation
Minus one	Inverse co-relation

R-square is calculated to predict the probability of co-relation between two variables.

R-value on day zero was 0.40, suggesting that there is a 16% ($R^2 = 0.16$) chance of co-relation between CRP and total WBC counts. Similarly on day three R-value was

0.42, suggestive of a 17.8% (R^2 = 0.178) chance of co-relation between CRP and total WBC counts.

On day seven, R- value was 0.13, suggesting that there is a 1.9% (R^2 = 0.019) chance of co-relation between CRP and total WBC counts.

The p-values on day zero, day three and day seven were 0.052, 0.056 and 0.561 respectively. All the values were higher than 0.05. Hence, they were statistically not significant.

In a similar study done by A. Galloway et al (88), between September 1982 and May 1983 on 16 spinal cord injury patients, they opined that, CRP levels fell to the normal range with successful treatment of UTI. An elevated CRP value is an unequivocal evidence of on-going inflammatory process, but the values should be interpreted only in the presence of full clinical information. They also were of the opinion that, increased CRP levels in the presence of clinical suspicion of UTI and absence of other known sites or sources of inflammation or infection, indicates urinary tract infection which requires treatment with antibiotics. They concluded that serial CRP monitoring will be helpful in monitoring the response to treatment and may aid in diagnosing UTI in the presence of clinical symptoms.

The results of the present study, was similar to the results of the above mentioned study. CRP can be used to monitor response to treatment. However, CRP can be used as a surrogate marker to detect UTI, in addition to clinical symptoms and if all other sources of inflammation or infection are ruled out.

Conclusion:

C-reactive protein is a good marker to assess response to treatment as it falls in a linear fashion with the appropriate treatment.

C-reactive protein is a non-specific marker of inflammation. However, in addition to clinical symptoms, it can be used as a marker for detecting urinary tract infection in spinal cord injury patients. It should be kept in mind that all other sources of infection or inflammation should be excluded before attributing the raised CRP levels to urinary tract infection.

Co-relation between CRP and total WBC counts was not significant probably due to the small sample size.

Limitations of the study:

The calculated sample size could not be reached due to time and logistical constraints. During the course of the study, co-relation between CRP and total WBC counts was calculated and was not significant probably owing to the low sample size. 26 out of the 27 patients received urine culture sensitivity appropriate antibiotics, hence variation in CRP levels in patients receiving culture non-specific antibiotics were not available for observation and comparison. Absence of a comparative neurologically normal population with UTI was another limitation of the study.

Future plan for the study:

We plan to continue the study till we reach the calculated sample size of 138 patients. A randomised control trial can be done to see the CRP levels, with one arm of patients receiving culture appropriate antibiotics and another arm with patients receiving culture non-specific antibiotics. A separate study can be done, comparing CRP with total WBC counts in patients with any infection and not specifically UTI. CRP levels can be studied in patients with SCI, to determine if elevated levels of CRP without any clinical symptoms can be indicative of UTI or only asymptomatic colonisation of the bladder. A comparative study can be done in neurologically intact patients with UTI and persons with SCI with UTI, to see if there is any difference in the way of fall in CRP levels with appropriate treatment.

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Annexures:

1. Institutional review board(IRB) acceptance letter
2. Patient information sheet
3. Informed consent form
4. Clinical research form
5. Patient Data – Excel format

IRB acceptance letter:

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho MS Ortho DNB Ortho.
Chairperson, Research Committee & Principal

Dr. Biju George, MBBS., MD., DM
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

April 27, 2016

Dr Ranjan S S,
PG Registrar,
Department of PMR,
Christian Medical College,
Vellore 632 004.

Sub: **Fluid Research Funding: New Proposal**
Evaluation of the usefulness of C-reactive protein as a marker of urinary tract infection and its response to treatment in persons with spinal cord injury.
Dr Ranjan S S, Emp. No: 21206, PG Registrar, Dr Henry Prakash, Emp. No: 20322, Department of Physical medicine and Rehabilitation (PMR),Dr. John Antony Jude Prakash, Emp. No: 14982, Professor, Dr. Rani Diana Sahni, Emp. No: 30969, Associate professor, Department of Microbiology.
Mr. Bijesh Yadav, Emp. No: 3324, Senior Demonstrator, Department of Biostatistics.

Ref: IRB Min No: 9916 [OBSERVE] dated 05.02.2016

Dear Dr Ranjan S S,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Evaluation of the usefulness of C-reactive protein as a marker of urinary tract infection and its response to treatment in persons with spinal cord injury" on February 05th 2016.

The Committee reviewed the following documents:

1. IRB Application format
2. Patient Information Sheet and Informed Consent Form (English, Tamil)
3. Cvs of Drs. Ranjan, Henry Prakash, Rani Diana Sahni, John Antony Jude Prakash, Bijesh Yadav
4. No. of documents 1 - 3

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on February 05th 2016 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

2 of 4

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho MS Ortho DNB Ortho.
Chairperson, Research Committee & Principal

Dr. Biju George, MBBS., MD., DM
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Name	Qualification	Designation	Affiliation
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, Research), Additional Vice Principal , Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC,Vellore	Internal, Clinician
Dr. Nihal Thomas	MD, MNAMS, DNB (Endo), FRACP (Endo) FRCP(Edin) FRCP (Glasg)	Professor & Head, Endocrinology. CMC, Vellore	Internal, Clinician
Dr. Jayaprakash Muliyil	BSc, MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, Vellore	External, Scientist &Epidemiologist
Rev. Joseph Devaraj	BSc, BD	Chaplaincy Department, CMC, Vellore	Internal, Social Scientist
Dr. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician
Dr. Visalakshi. J	MPH, PhD	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Mrs. Sheela Durai	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Dr. Niranjan Thomas	DCH, MD, DNB (Paediatrics)	Professor, Neonatology, CMC, Vellore	Internal, Clinician
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Dr. B. J. Prashantham	MA(Counseling Psychol MA(Theology), Dr. Min(Clinical Counselling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centr Vellore	External, Social Scientist
Dr. Ratna Prabha	MBBS, MD (Pharma)	Associate Professor, Clinical Pharmacology, CMC, Vellore	Internal, Pharmacologist

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
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Dr. Biju George, MBBS., MD., DM
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Mrs. Emily Daniel	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Dr. Vivek Mathew	MD (Gen. Med.) DM (Neuro) Dip. NB (Neuro)	Professor, Neurology, CMC, Vellore	Internal, Clinician
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Dr. Inian Samarasam	MS, FRCS, FRACS	Professor, Surgery, CMC, Vellore	Internal, Clinician

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "Evaluation of the usefulness of C-reactive protein as a marker of urinary tract infection and its response to treatment in persons with spinal cord injury" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in)

Fluid Grant Allocation:

A sum of 50,000/- INR (Rupees Fifty thousand Only) will be granted for 12 months.

Yours sincerely

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD., DM.
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

IRB Min No: 9916 [OBSERVE] dated 05.02.2016 4 of 4

Patient information sheet

The study requires your blood sample to be drawn at three points of time.

The first sample will be drawn if you develop symptoms/signs of infection, before starting antibiotic treatment. Here again, blood samples are routinely taken as a part of clinical care, but on your consenting to participate, an additional 5ml of blood will be drawn for the purpose of the study.

The second sample will be taken 3 days (72 hours) from this, and the third another 3 days (72 hours) from the second sample.

What harm can I expect from the study?

The amount of blood drawn for the study is around 5ml at each of the 3 points of time. This is not known to cause any significant clinical problems. If in case you do experience any discomfort (nausea, light-headedness, generalized weakness), you will receive immediate medical attention.

The blood samples will be drawn under strict aseptic precautions, which mean that the chances of developing injection site infections are rare. In the event that you develop the same, it will be managed accordingly in the ward.

Will I be charged extra for the test performed under the study?

You will NOT be charged any additional fee for the test performed in the study and no incentives will be provided for your participation.

Will participation in the study change my treatment in any way?

No. Your treatment will NOT be affected in any way whether you choose to participate in the study or not. Your consent is purely voluntary.

Can I withdraw my consent even after starting the study?

Yes. You are free to withdraw your consent at ANY point of time during the study.

What benefits can I expect from the study?

The study may not provide any immediate benefit to you, but your participation will greatly contribute to the knowledge of the use of the marker under study in urinary tract infections in persons with spinal cord injury, and may eventually help deliver more cost-effective and efficient treatment to them.

By participating in the study, you agree to share information about yourself, including your past medical and surgical history, and answer the questions that the investigators ask you about your symptoms and consent for drawing blood if urinary tract infection is suspected during your admission under Department of Physical Medicine and Rehabilitation in CMC, Vellore. It also means that we are allowed to obtain your lab reports. The investigators may publish the information they get from the study, but your identity will be kept confidential.

In case of any queries, you can contact:

Dr Ranjan S S,
PG registrar, Department of PMR,
CMC, Vellore – 632004
Phone No. 7094326316 Email: ranjan.sham@cmcvellore.ac.in

<u>Informed Consent Form for Subjects</u>:

Informed Consent form to participate in a research study

Study Title: Evaluation of the usefulness of C-reactive protein as a marker of urinary tract infection and its response to treatment in persons with spinal cord injury.

Study Number: _____

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age: _____

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: _____ Signature:

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature or thumb impression of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness: _____

Clinical Research Form

Evaluation of the usefulness of C-reactive protein as a marker of urinary tract infection and its response to treatment in persons with spinal cord injury.

Study number:

Name:

Age:

Sex:

Hospital number:

Address:

Diagnosis:

Mode of spinal cord injury: Traumatic/non-traumatic

Duration of injury:

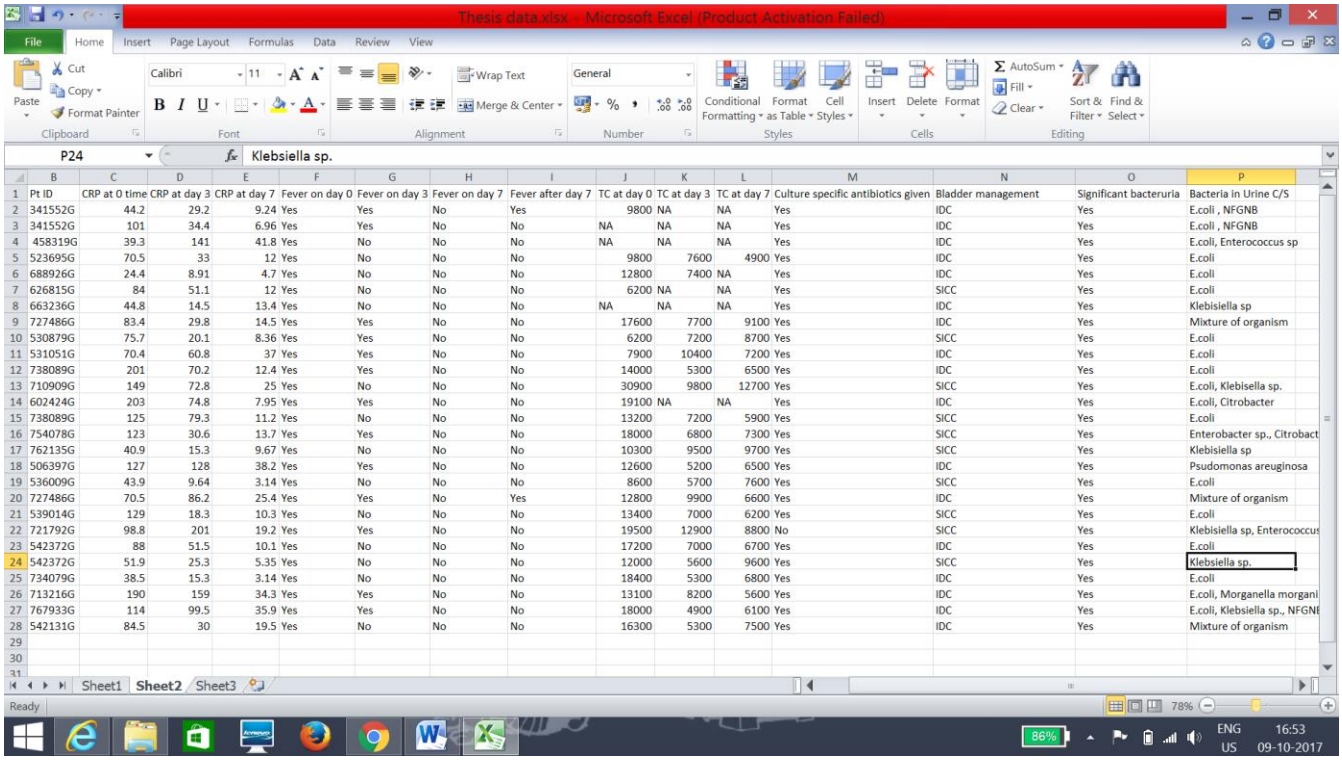
Bladder management: Indwelling urethral catheter / CIC

	At suspicion of UTI, before starting the treatment (Day 0)	72 hours after starting of treatment (Day 3)	After another 72 hours (day 7)
CRP level			
Total WBC level			

Form completed by: Name and signature

Date:

Patient data in excel format:



Pt ID	CRP at 0 time	CRP at day 3	CRP at day 7	Fever on day 0	Fever on day 3	Fever on day 7	Fever after day 7	TC at day 0	TC at day 3	TC at day 7	Culture specific antibiotics given	Bladder management	Significant bacteruria	Bacteria in Urine C/S
341552G	44.2	29.2	9.24	Yes	Yes	No	Yes	9800	NA	NA	Yes	IDC	Yes	E.coli , NFGNB
341552G	101	34.4	6.96	Yes	Yes	No	No	NA	NA	NA	Yes	IDC	Yes	E.coli , NFGNB
458319G	39.3	141	41.8	Yes	No	No	No	NA	NA	NA	Yes	IDC	Yes	E.coli, Enterococcus sp
523695G	70.5	33	12	Yes	No	No	No	9800	7600	4900	Yes	IDC	Yes	E.coli
688926G	24.4	8.91	4.7	Yes	No	No	No	12800	7400	NA	Yes	IDC	Yes	E.coli
626815G	84	51.1	12	Yes	No	No	No	6200	NA	NA	Yes	SICC	Yes	E.coli
663236G	44.8	14.5	13.4	Yes	No	No	No	NA	NA	NA	Yes	IDC	Yes	Klebsiella sp
727486G	83.4	29.8	14.5	Yes	Yes	No	No	17600	7700	9100	Yes	IDC	Yes	Mixture of organism
530879G	75.7	20.1	8.36	Yes	Yes	No	No	6200	7200	8700	Yes	SICC	Yes	E.coli
531051G	70.4	60.8	37	Yes	Yes	No	No	7900	10400	7200	Yes	IDC	Yes	E.coli
738089G	201	70.2	12.4	Yes	Yes	No	No	14000	5300	6500	Yes	IDC	Yes	E.coli
710909G	149	72.8	25	Yes	No	No	No	30900	9800	12700	Yes	SICC	Yes	E.coli, Klebisella sp.
602424G	203	74.8	7.95	Yes	Yes	No	No	19100	NA	NA	Yes	IDC	Yes	E.coli, Citrobacter
738089G	125	79.3	11.2	Yes	No	No	No	13200	7200	5900	Yes	SICC	Yes	E.coli
754078G	123	30.6	13.7	Yes	Yes	No	No	18000	6800	7300	Yes	SICC	Yes	Enterobacter sp., Citrobact
762135G	40.9	15.3	9.67	Yes	No	No	No	10300	9500	9700	Yes	SICC	Yes	Klebisiella sp
506397G	127	128	38.2	Yes	Yes	No	No	12600	5200	6500	Yes	IDC	Yes	Psudomonas areuginosa
536009G	43.9	9.64	3.14	Yes	No	No	No	8600	5700	7600	Yes	SICC	Yes	E.coli
727486G	70.5	86.2	25.4	Yes	Yes	No	Yes	12800	9900	6600	Yes	IDC	Yes	Mixture of organism
539014G	129	18.3	10.3	Yes	No	No	No	13400	7000	6200	Yes	SICC	Yes	E.coli
721792G	98.8	201	19.2	Yes	Yes	No	No	19500	12900	8800	No	SICC	Yes	Klebisiella sp, Enterococcus
542372G	88	51.5	10.1	Yes	No	No	No	17200	7000	6700	Yes	IDC	Yes	E.coli
542372G	51.9	25.3	5.35	Yes	No	No	No	12000	5600	9600	Yes	SICC	Yes	Klebsiella sp.
734079G	38.5	15.3	3.14	Yes	No	No	No	18400	5300	6800	Yes	IDC	Yes	E.coli
713216G	190	159	34.3	Yes	Yes	No	No	13100	8200	5600	Yes	IDC	Yes	E.coli, Morganella morgani
767933G	114	99.5	35.9	Yes	Yes	No	No	18000	4900	6100	Yes	IDC	Yes	E.coli, Klebsiella sp., NFGNB
542131G	84.5	30	19.5	Yes	No	No	No	16300	5300	7500	Yes	IDC	Yes	Mixture of organism